Protective Groups in Synthetic Organic Chemistry

Lecture Notes

Key Texts

P. J. Kocienski, Protecting Groups (2nd Edition), 1994, Georg Thieme Verlag: Stuttgart, p. 260.

P. J. Kocienski, Protecting Groups (3rd Edition), 2004, Georg Thieme: Stuttgart, p. 679.

T. W. Greene, P. G. M. Wutz, Protective Groups in Organic Synthesis (3rd Edition), 1999, John Wiley and Sons: New York, p. 779.

Key Reviews

Selective Deprotections: T. D. Nelson, R. D. Crouch, Synthesis 1996, 1065.

Protective Groups: Background and General Considerations

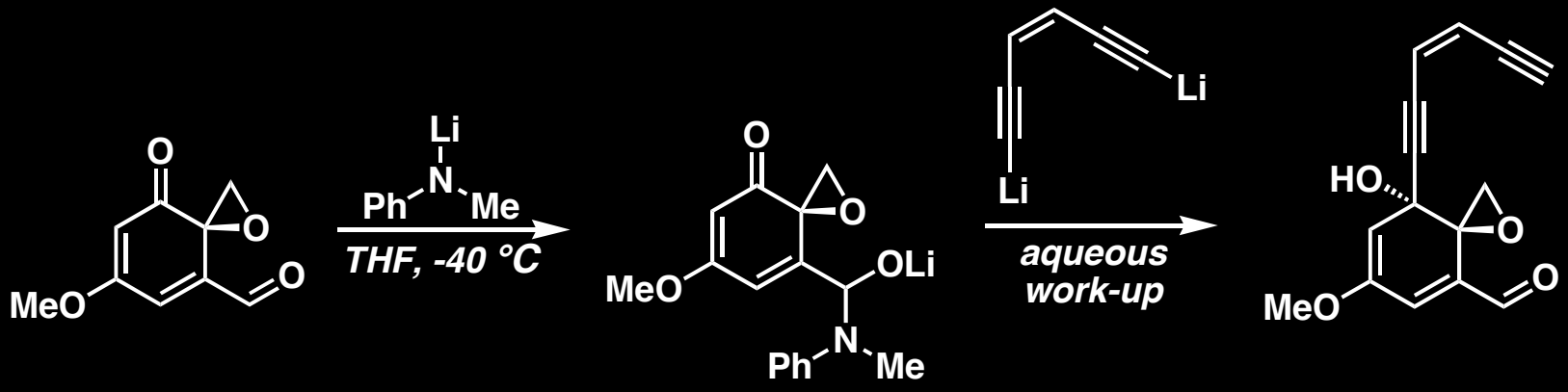
"Protection is a principle, not an expedient"
Benjamin Disraeli, British Prime Minister, 1845

"Like death and taxes, protecting groups have become a consecrated obstruction which we cannot elude"
Peter Kocienski, Organic Chemist

Remember:

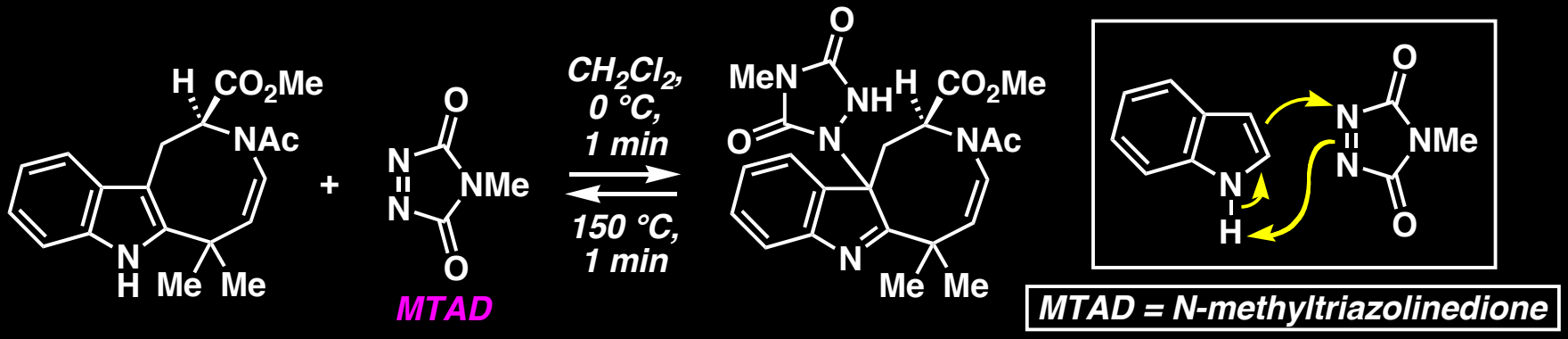
- *Every protecting group adds at least one, if not two steps to a synthesis*
- *They only detract from the overall efficiency and beauty of a route, but, without them, there are certainly transformations which we would not be able to do at all.*

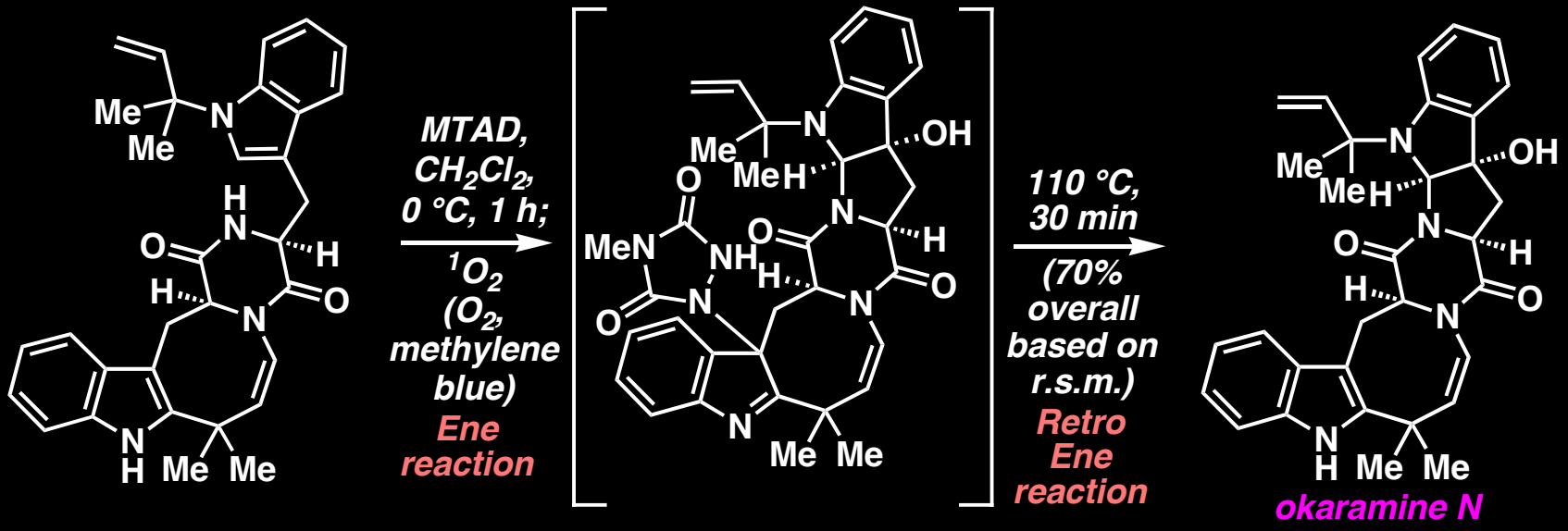
Protective Groups: Temporary Protection



Temporary protection involves the ideal for protecting groups when they are required: the protection step, desired reaction, and deprotection all occur in the same pot.

Ene Reactions in Total Synthesis: Ene/Retro-Ene Sequence to Protect Indole





P. S. Baran, C. A. Guerrero, E. J. Corey, J. Am. Chem. Soc. 2003, 125, 5628.
P. S. Baran, C. A. Guerrero, E. J. Corey, Org. Lett. 2003, 5, 1999.

Protective Groups: Background and General Considerations

Tactical considerations to consider for each protecting group selected in a synthesis:

It should be easily and efficiently introduced.

It should be cheap and readily available.

It should be easy to characterize and avoid the introduction of new stereogenic centers.

It should not afford so many spectroscopic signals that it hides key resonances for the substrate.

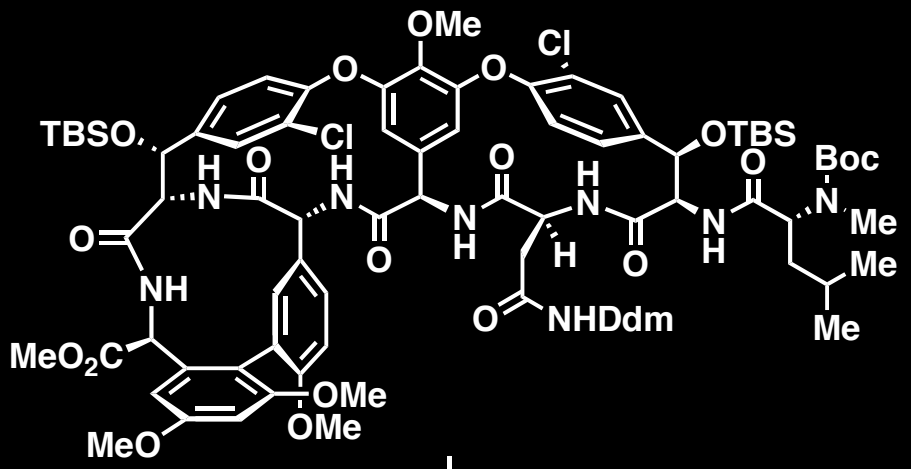
It should be stable to chromatography.

It should be stable to a wide range of reaction conditions.

It should be removed selectively and efficiently under highly specific conditions.

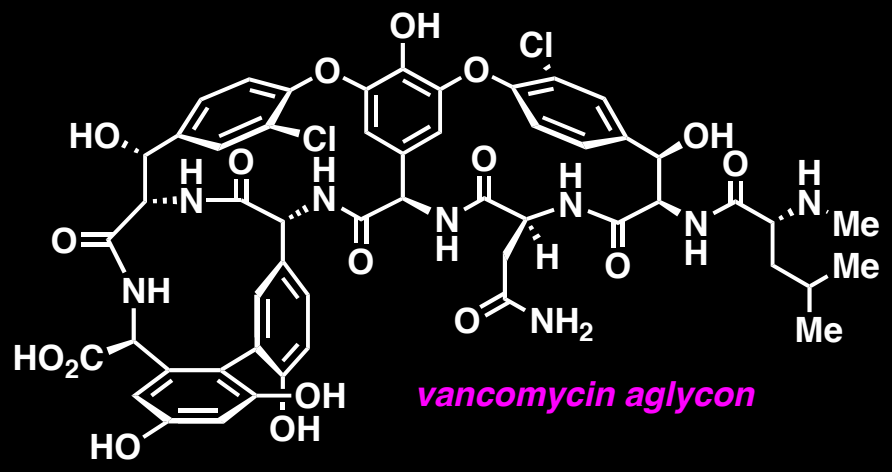
The by-products of deprotection shoud be easily separated from the substrate.

Protective Groups: Something to be Very Carefully Considered



(62% overall)
Global deprotections

1. HF•py/py, THF, 0→25 °C, 12 h
2. $AlBr_3$, $EtSH/CH_2Cl_2$ (1:1), 25 °C, 4 h

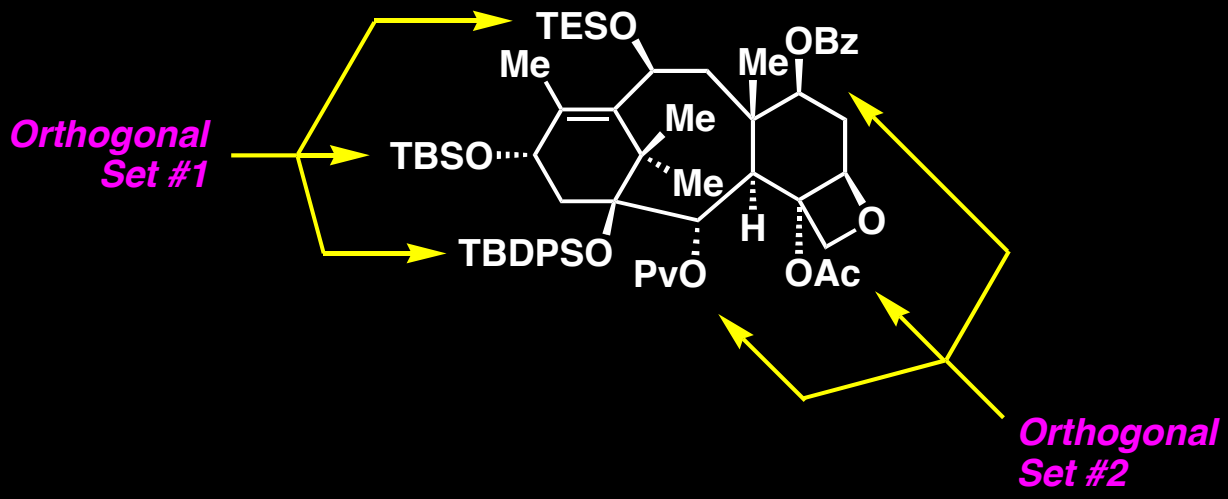


vancomycin aglycon

K. C. Nicolaou and co-workers, Angew. Chem. Int. Ed. 1998, 37, 2708.

Protective Groups: Orthogonal Sets of Protecting Groups

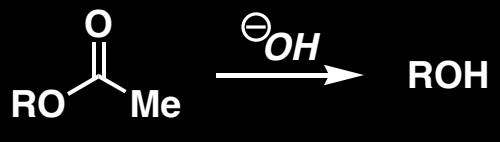
Orthogonal Set = a groups of protecting groups whose removal is accomplished in any order with reagents and conditions that do not affect protecting groups in any other orthogonal set.

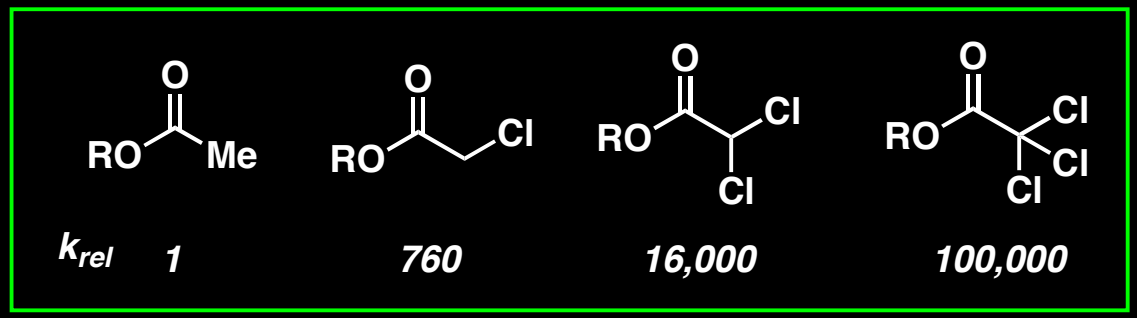


In practice this concept is incredibly difficult to reduce to practice, but it is a useful framework and organizing principle to think about protecting group regimes for a complex molecule synthesis.

Protective Groups:
Orthogonal Sets of Protecting Groups

1. Cleavage by basic solvolysis





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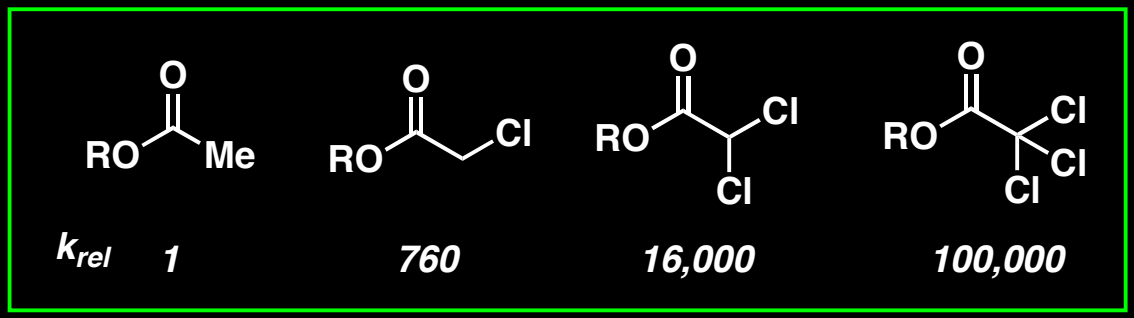
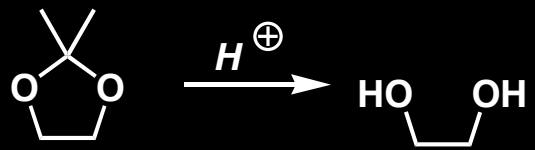


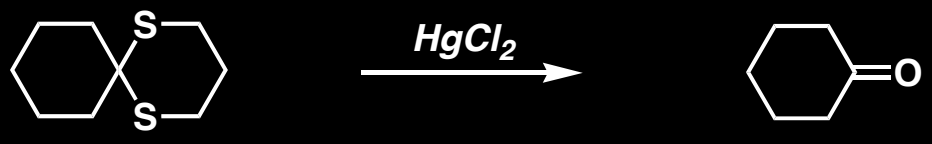
2. Cleavage by acidic hydrolysis



Other groups easily cleaved by acid

Protective Groups:
Orthogonal Sets of Protecting Groups

3. Cleavage by heavy metals



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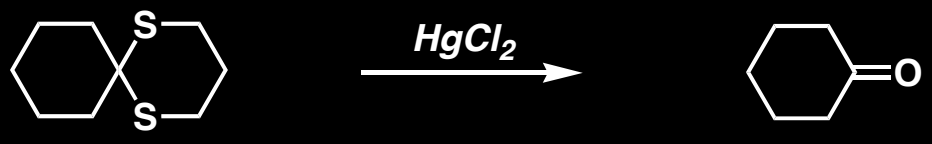
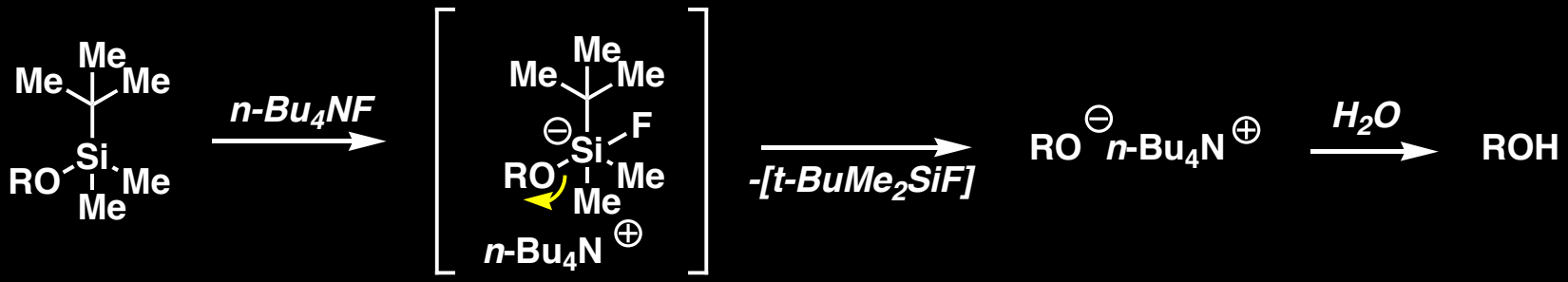


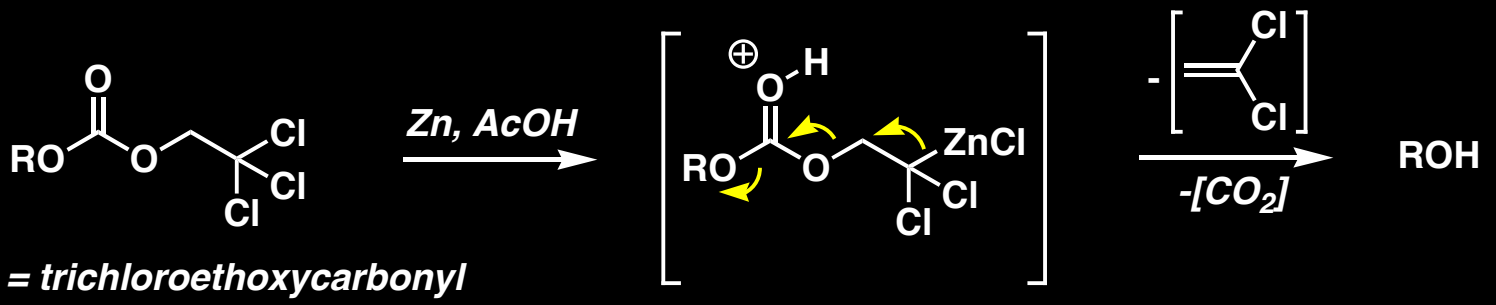
4. Cleavage by fluoride



Strength of Si-F bond is 810 kJ/mol while Si-O bond is 530 kJ/mol

Protective Groups: Orthogonal Sets of Protecting Groups

5. Reductive Elimination



Troc = trichloroethoxycarbonyl

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Orthogonal Sets of Protecting Groups

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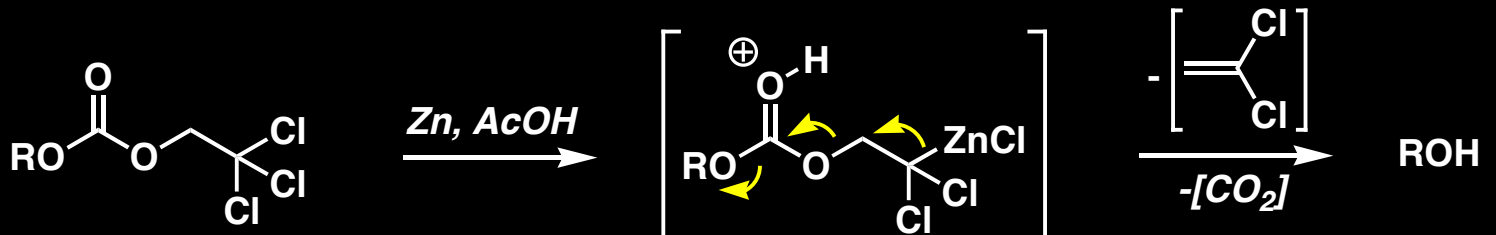
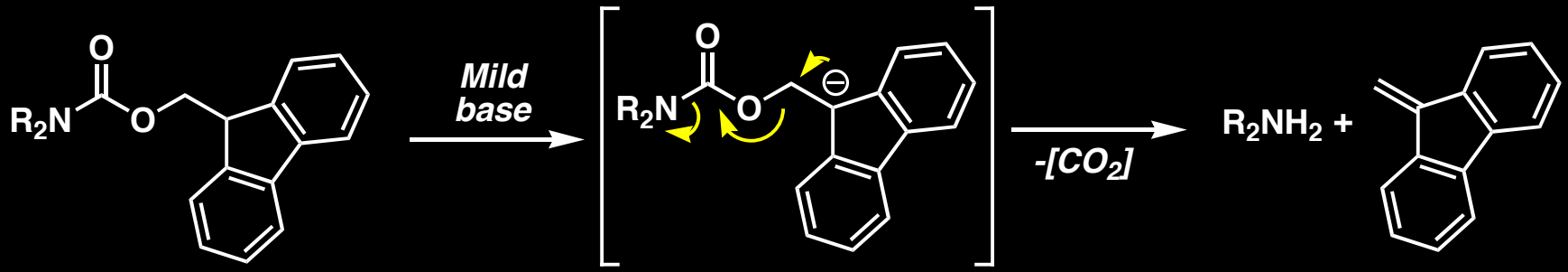


Troc = trichloroethoxycarbonyl

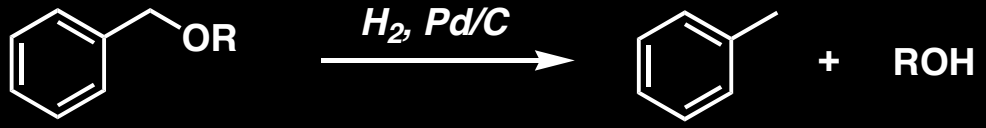
6. β-elimination



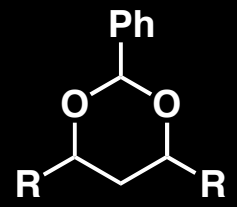
Fmoc = 9-fluorenylmethyl carbamate

Protective Groups: Orthogonal Sets of Protecting Groups

7. Hydrogenolysis



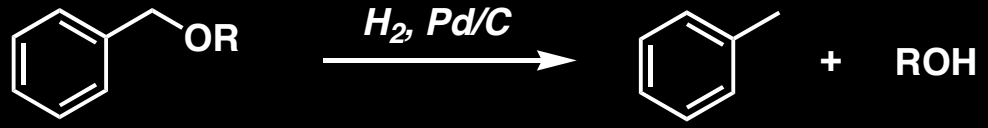
benzyl ether



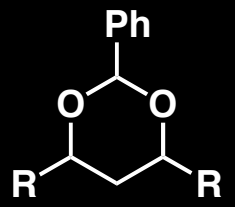
Other examples of cleavable groups

Protective Groups:
Orthogonal Sets of Protecting Groups

7. Hydrogenolysis

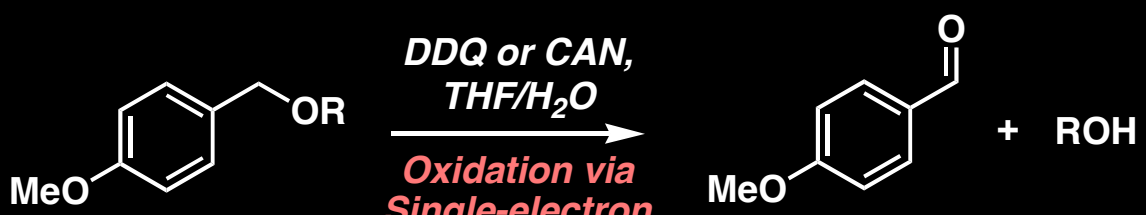


benzyl ether

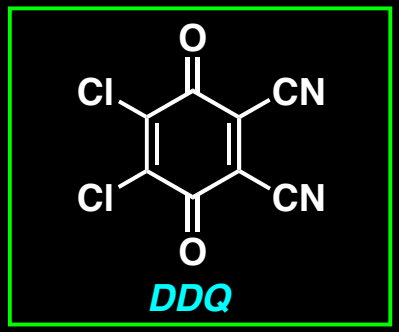


Other examples of cleavable groups

8. Oxidation

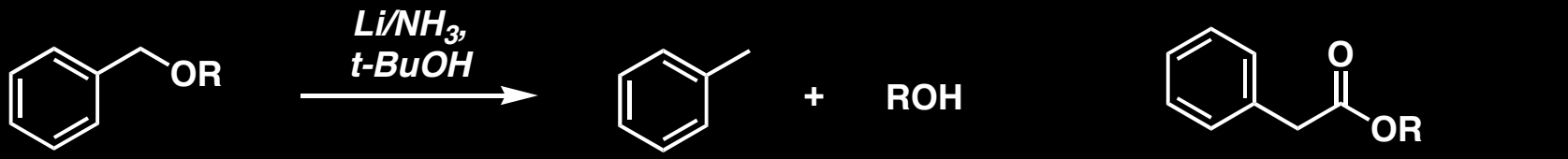


p-methoxybenzyl ether



Protective Groups: Orthogonal Sets of Protecting Groups

9. Dissolving Metal Reduction



Only other protecting group applicable to these conditions

Protective Groups: Orthogonal Sets of Protecting Groups

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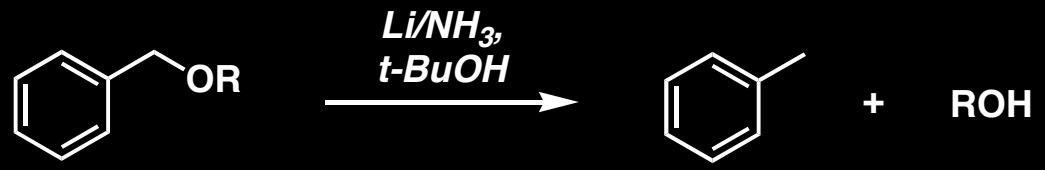
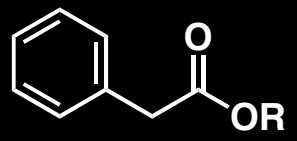




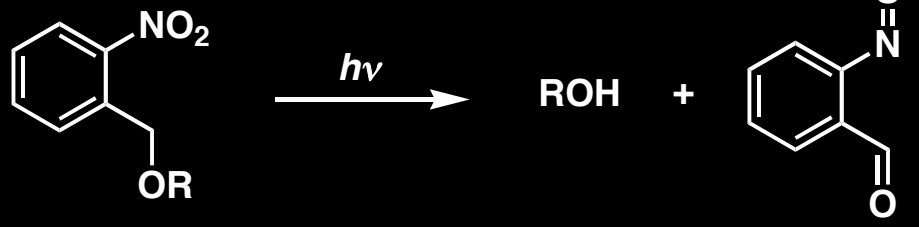
Only other protecting group applicable to these conditions

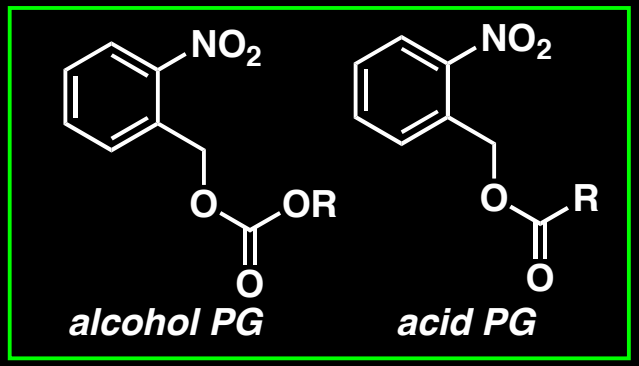
10. Transition Metal Catalysis (i.e. Allyl-based protecting groups)

Can also use $(Ph_3P)_3RhCl$ and acid

Protective Groups:
Orthogonal Sets of Protecting Groups

11. Light





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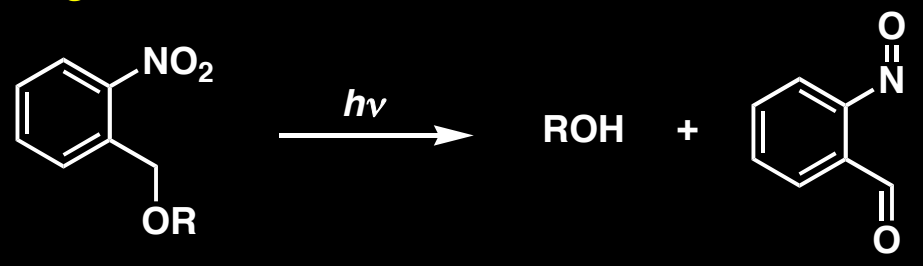
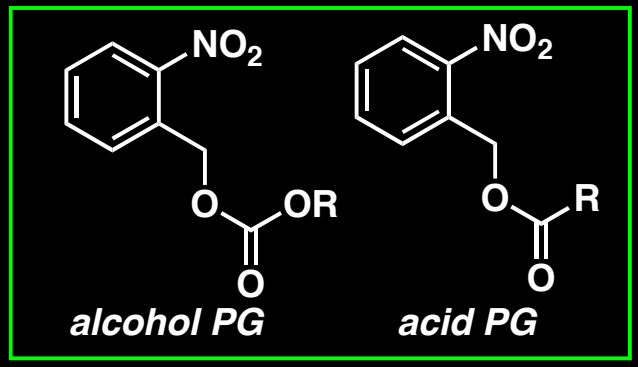
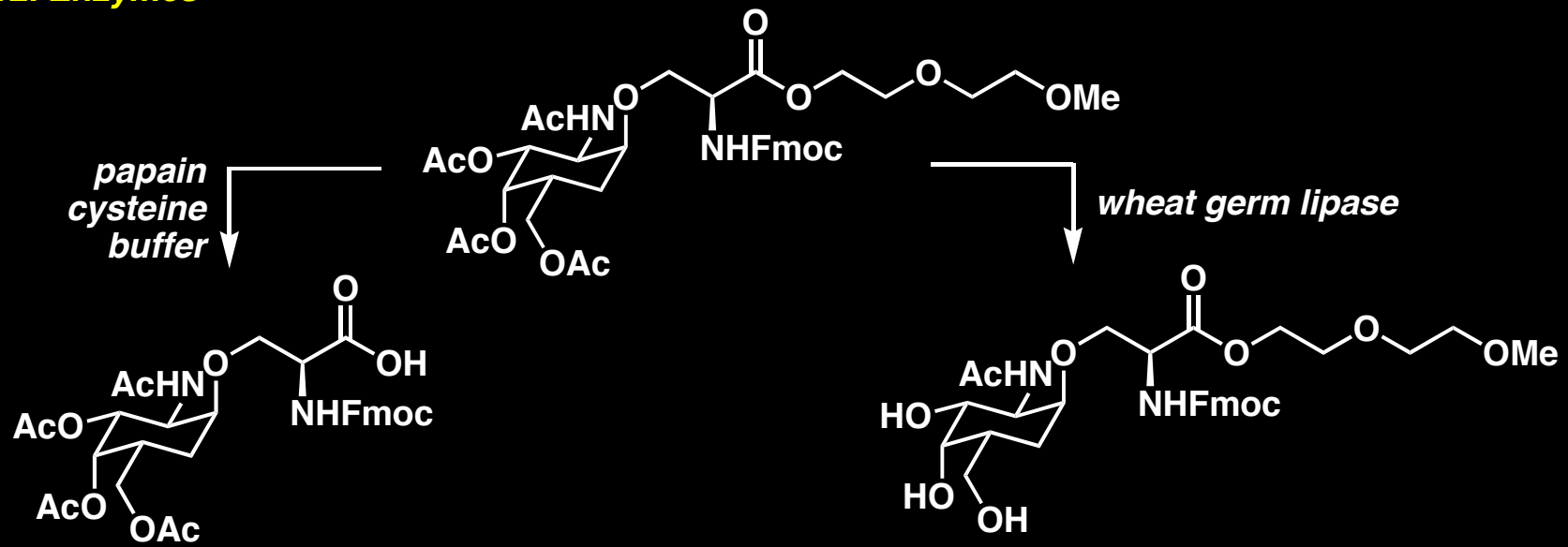
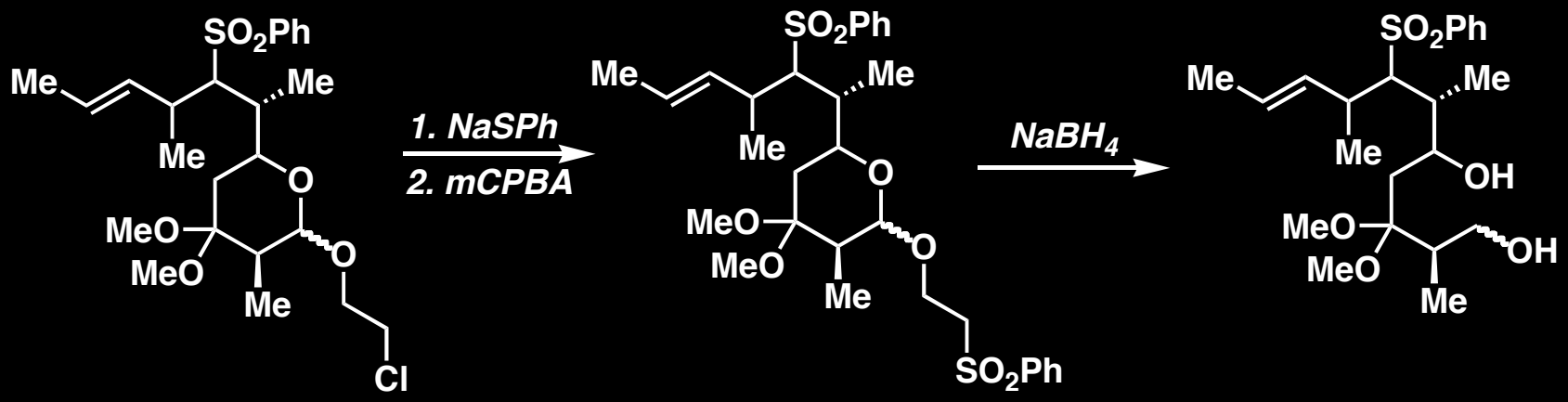




12. Enzymes



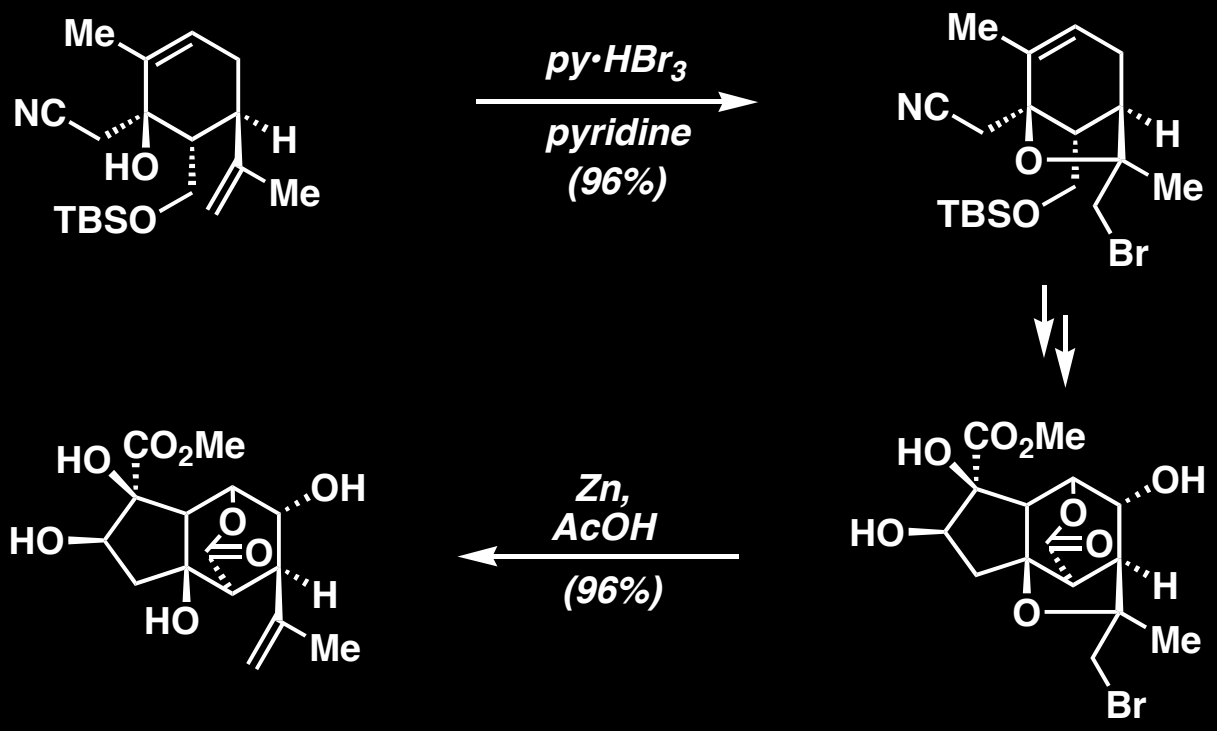
Protective Groups: Relay Deprotection



Relay deprotection: when a protecting group that is stable under most conditions is transformed chemically into a new, and more labile, protecting group.

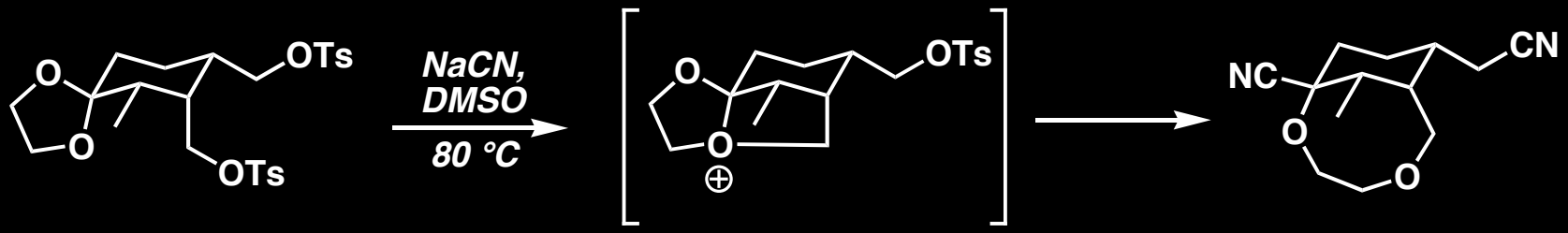
Protective Groups: Mutual Protection

"Une pierre, deux oiseaux"
"Zwei Fleigen mit einer Klappe schlagen"
"To kill two birds with one stone"



B. M. Trost, M. J. Krische, J. Am. Chem. Soc. 1999, 121, 6131.

Protective Groups: Sometimes Not-So-Innocent Bystanders



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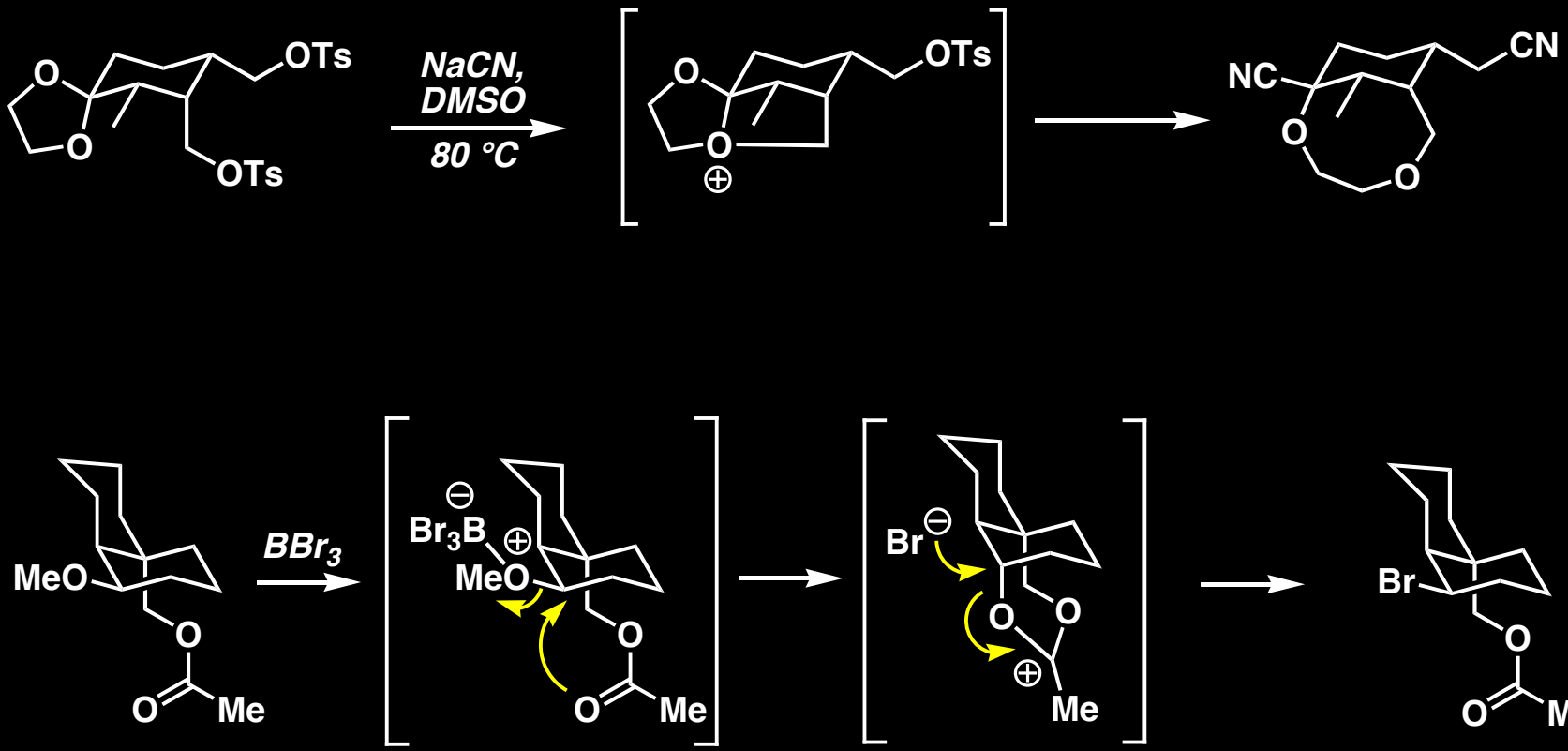
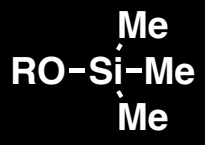
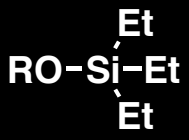


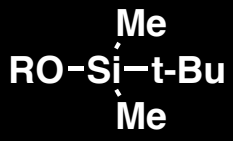
Hydroxyl Protecting Groups: Silyl Ethers



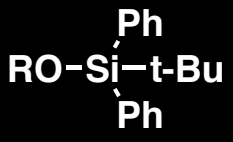
trimethylsilyl (TMS)



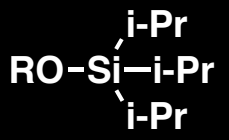
triethylsilyl (TES)



t-butyldimethylsilyl (TBS or TBDMS)



t-butyldiphenylsilyl (TBDPS)



triisopropylsilyl (TIPS)

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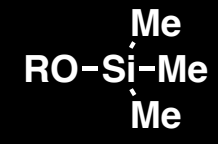
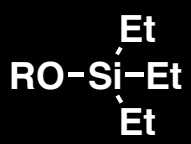
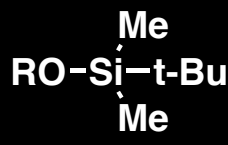
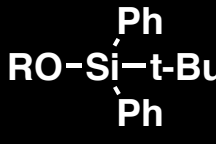
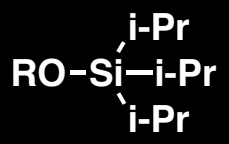
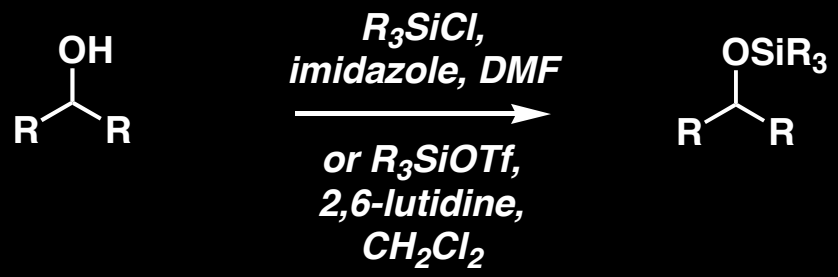
				
trimethylsilyl (TMS)	*triethylsilyl (TES)*	*t-butyldimethylsilyl (TBS or TBDMS)*	*t-butyldiphenylsilyl (TBDPS)*	*triisopropylsilyl (TIPS)*
Relative Acid Stability ***($t_{1/2}$ in 1% HCl/MeOH)***				
1 (<1 min)	*64 (<1 min)*	*20,000 (<1 min)*	*5,000,000 (255 min)*	*700,000 (55 min)*
Relative Base Stability ***($t_{1/2}$ in 5% NaOH/MeOH)***				
1 (<1 min)	*10 - 100 (1 min)*	*20,000 (> 24 h)*	*20,000 (> 24 h)*	*100,000 (> 24 h)*

Hydroxyl Protecting Groups: Silyl Ethers

Formation:



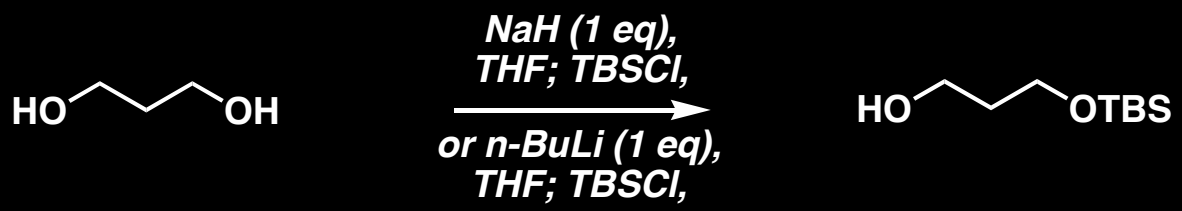
Cleavage:

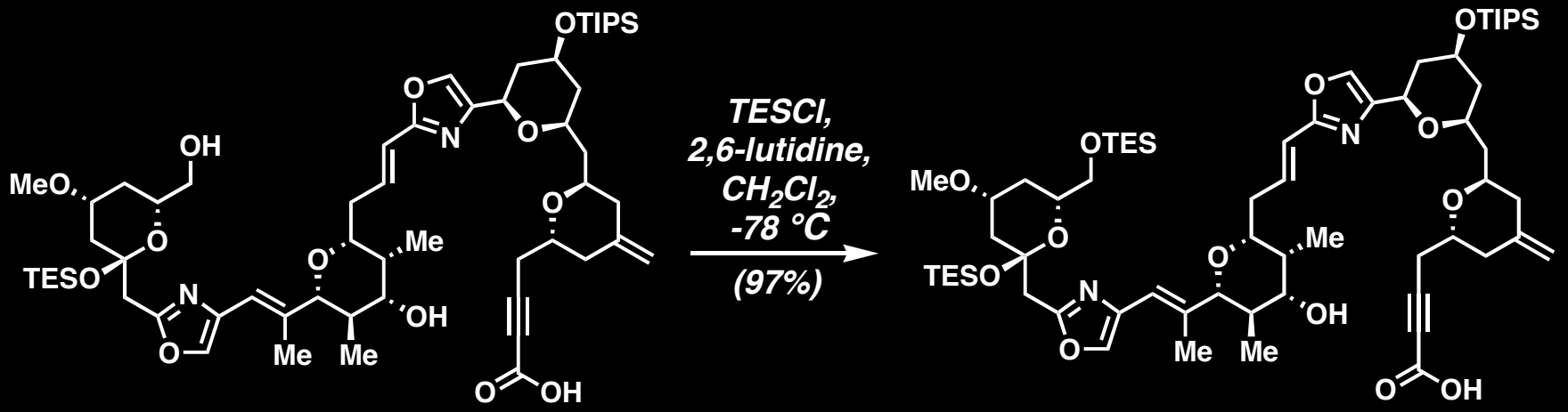
Common Fluoride Sources

HF
3HF•NEt$_3$
HF•pyr
n-Bu$_4$NF (TBAF)/AcOH
HF•pyr/pyr
n-Bu$_4$NF (TBAF)

Hydroxyl Protecting Groups: Silyl Ethers

Selective Monosilylation of Diols is Possible:



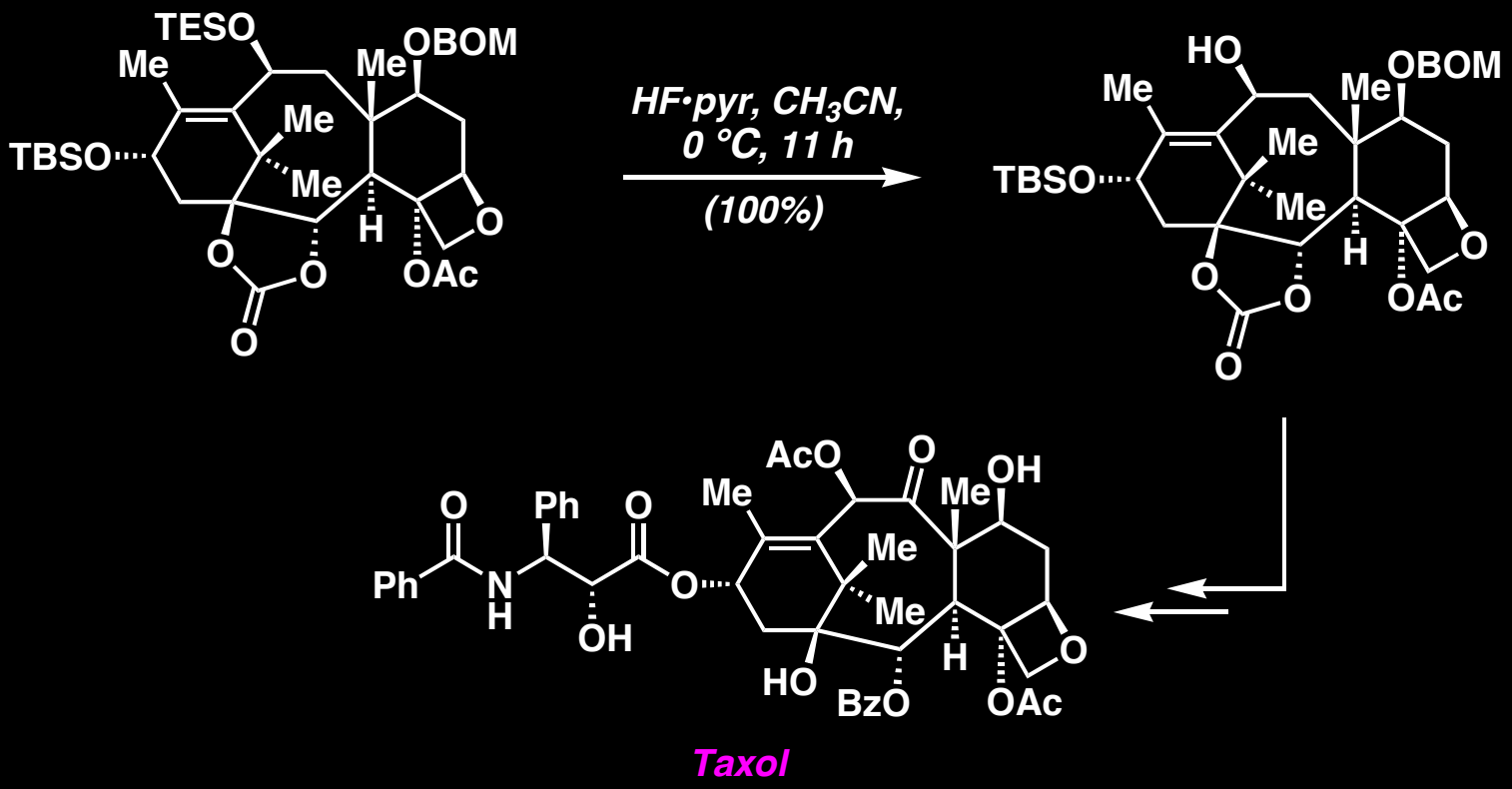


TESCl/imid and TESOTf/2,6-lutidine gave bis-silylated product

D. A. Evans, D. M. Fitch, Angew. Chem. Int. Ed. 2000, 39, 2536.

Hydroxyl Protecting Groups: Silyl Ethers

Selective Deprotection of Silyl Ethers is Also Possible:

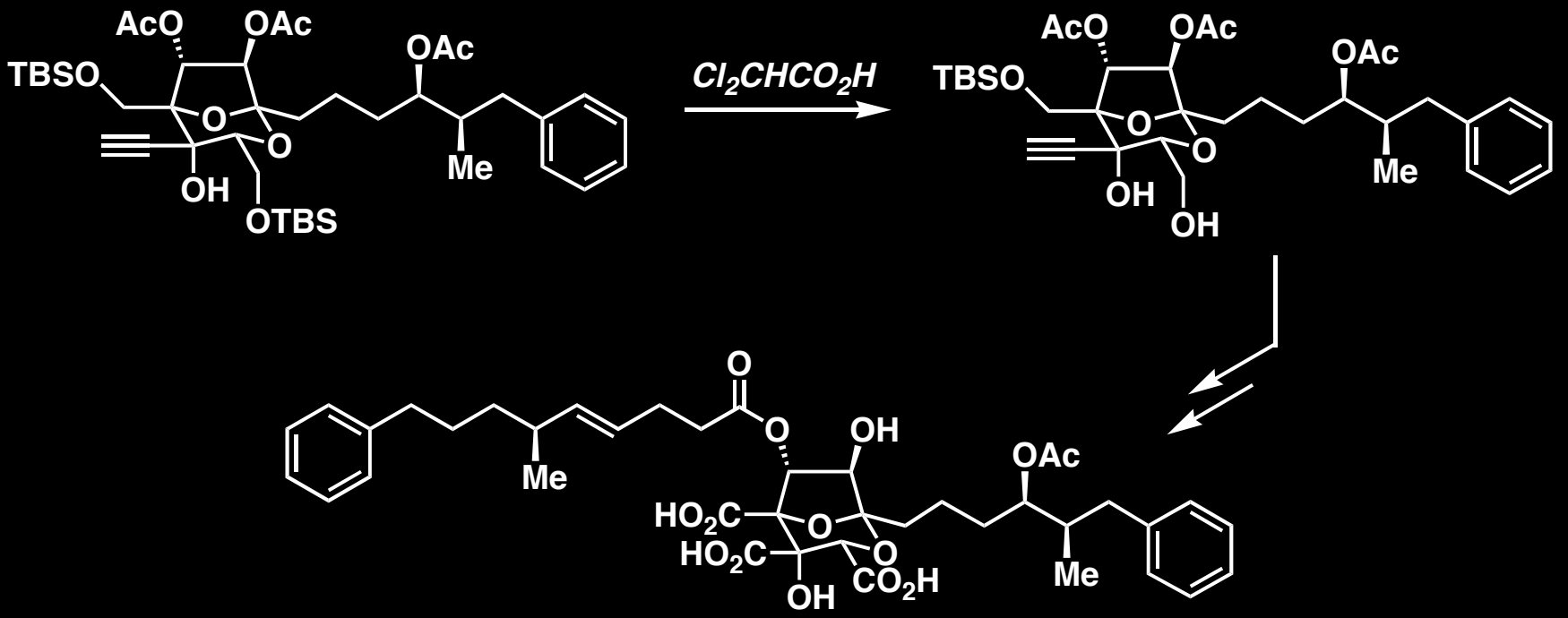


Taxol

R. A. Holton and co-workers, J. Am. Chem. Soc. 1994, 116, 1599.

Hydroxyl Protecting Groups: Silyl Ethers

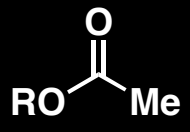
Selective Deprotection of Silyl Ethers is Also Possible:



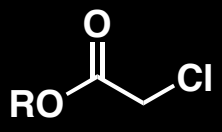
zaragozic acid

E. M. Carreira, J. DuBois, J. Am. Chem. Soc. 1995, 117, 8106.

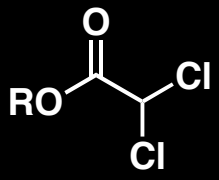
Hydroxyl Protecting Groups: Esters and Carbonates



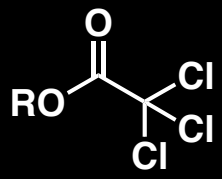
acetate (Ac)



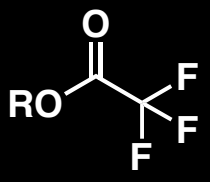
chloroacetate



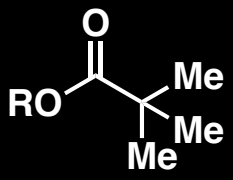
dichloroacetate



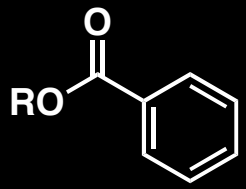
trichloroacetate



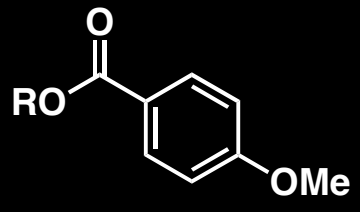
trifluoroacetate



pivaloate (Pv)



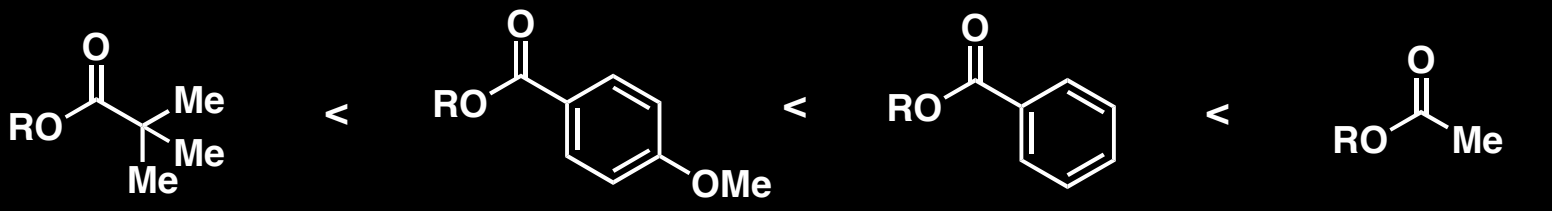
benzoate (Bz)



p-methoxybenzoate

Hydroxyl Protecting Groups: Esters and Carbonates

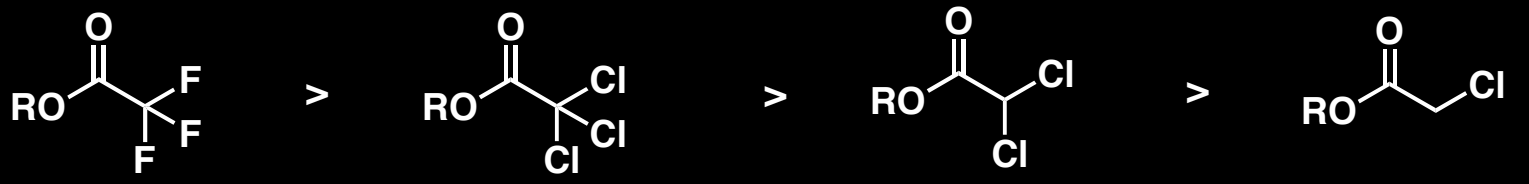
In general, the ease with which esters hydrolyze under basic conditions increases with the acidity of the product acid. Sterics also can play a role (i.e. pivaloate group)



pivaloate (Pv) *p-methoxybenzoate* *benzoate (Bz)* *acetate (Ac)*

[most stable]

∧

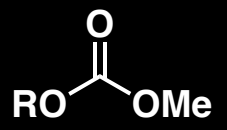


trifluoroacetate *trichloroacetate* *dichloroacetate* *chloroacetate*

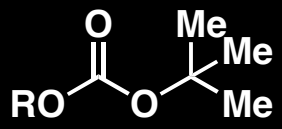
[least stable]

All can hydrolyze under acidic conditions, but typically only when water is present.

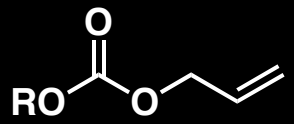
Hydroxyl Protecting Groups: Esters and Carbonates



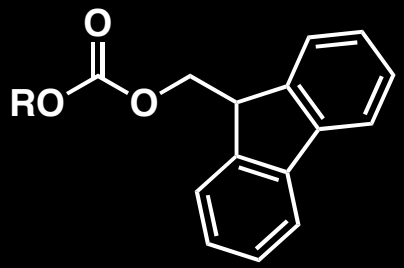
methyl carbonate



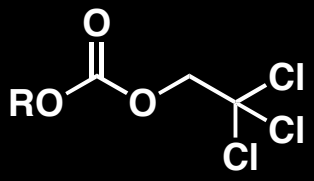
t-butylcarbonate (Boc)
[resistant to nucleophilic attack]



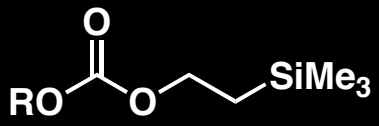
allyl carbonate (Alloc)
[cleaved with Pd/Nu]



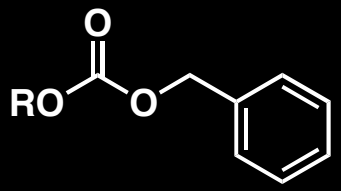
9-(fluorenylmethyl) carbonate (Fmoc)
[cleaved by mild base]



2,2,2-trichloroacetyl carbonate (Troc)
[cleaved with Zn/HOAc]



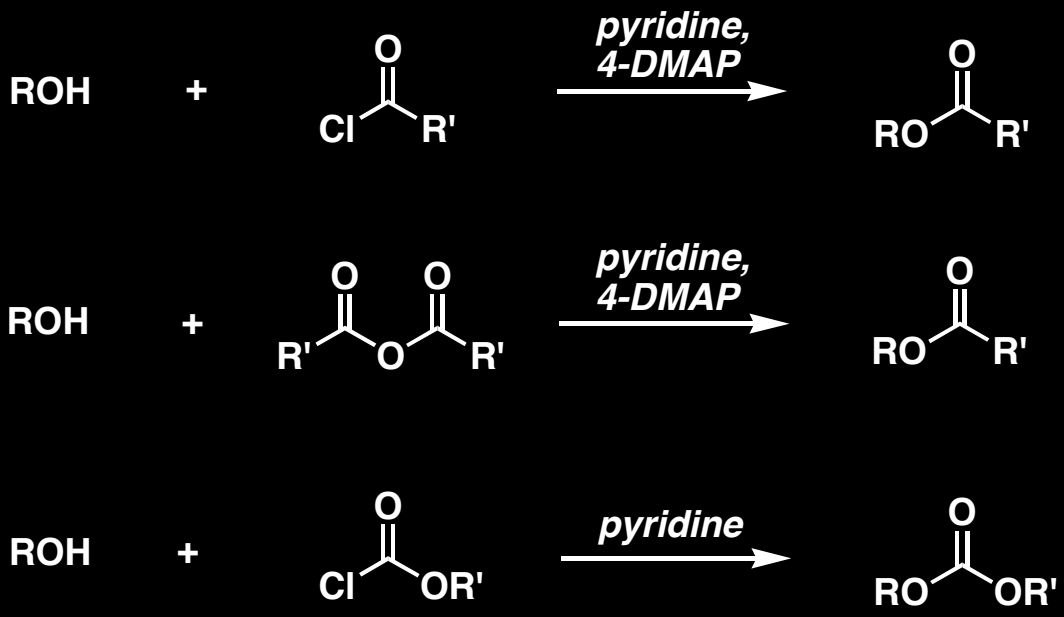
2-(trimethylsilyl) ethyl carbonate (Teoc)
[cleaved with fluoride]



benzyl carbonate (Cbz)
[cleaved by hydrogenolysis]

Hydroxyl Protecting Groups: Esters and Carbonates

General methods for the formation of esters and carbonates:



B. Neises, W. Steglich, Angew. Chem. Int. Ed. Engl. 1978, 17, 522.

Hydroxyl Protecting Groups: Esters and Carbonates

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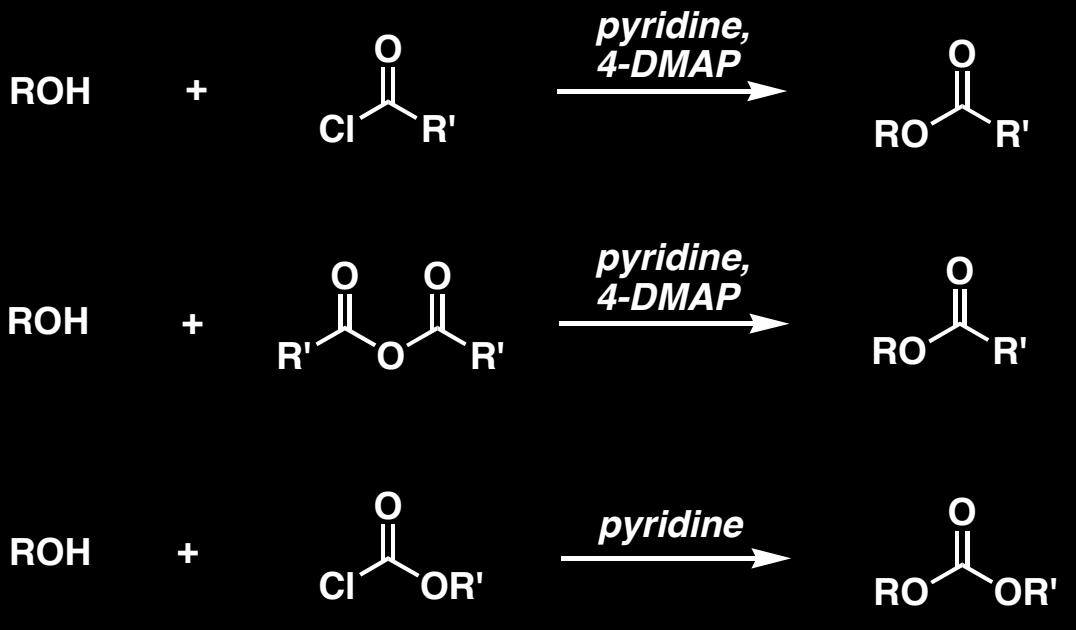
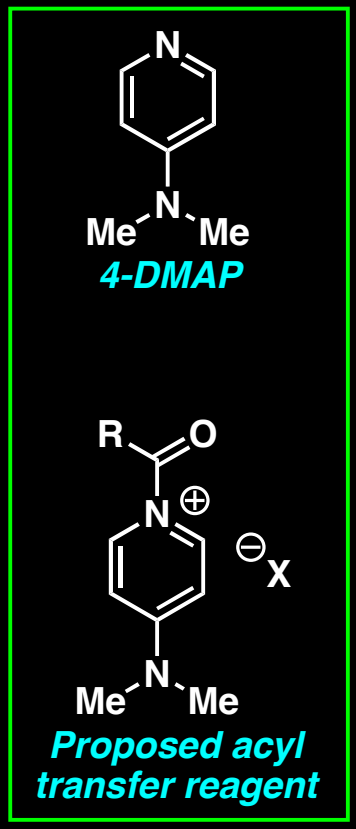
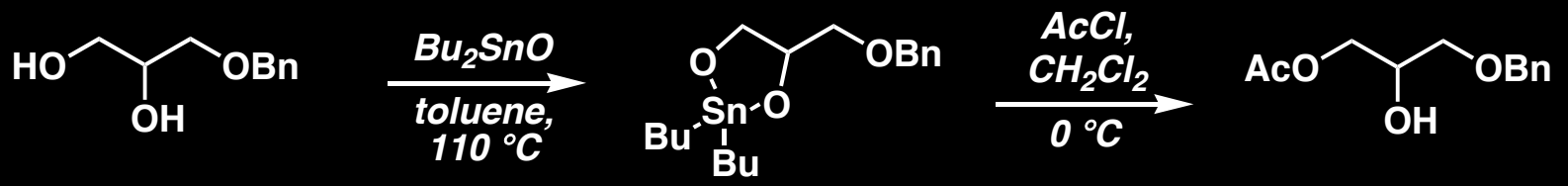




B. Neises, W. Steglich, Angew. Chem. Int. Ed. Engl. 1978, 17, 522.

Hydroxyl Protecting Groups: Esters and Carbonates

Tricks for selective formation of an ester from diol starting materials:



For a review, see: S. Hanessian, S. David, Tetrahedron, 1985, 41, 643.

Hydroxyl Protecting Groups: Esters and Carbonates

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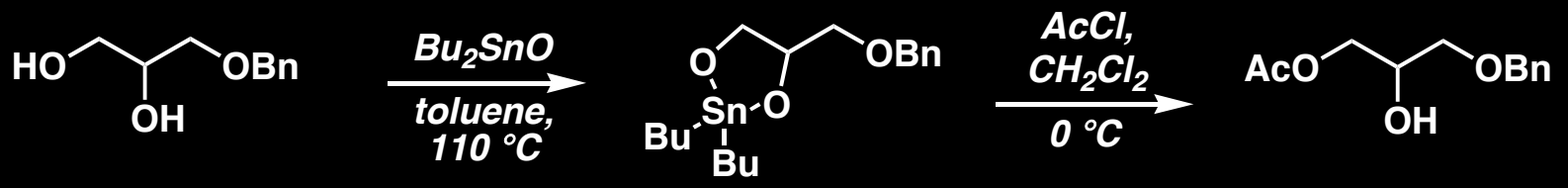
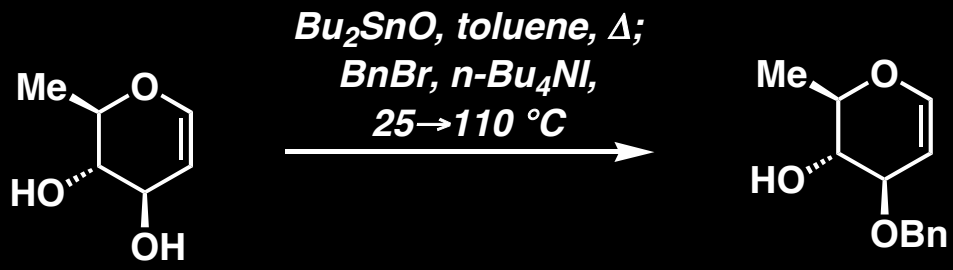


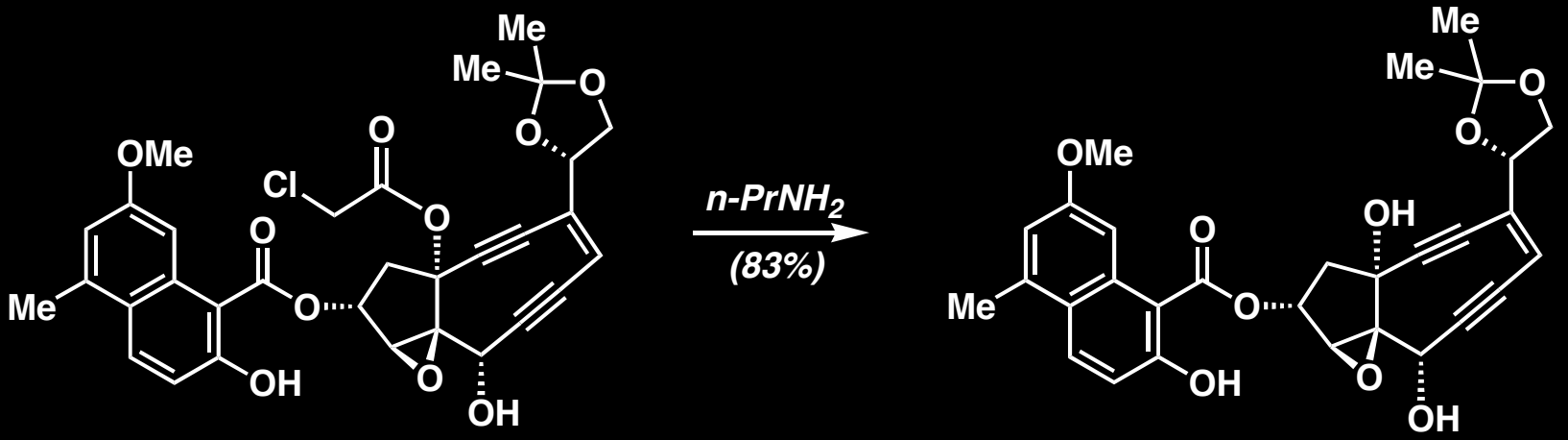


The sterically least encumbered position is always protected selectively; on sugars, if both positions are secondary and sterics are roughly equal, an equatorial alcohol will be protected selectively over an axially disposed alcohol.

For a review, see: S. Hanessian, S. David, Tetrahedron, 1985, 41, 643.

Hydroxyl Protecting Groups: Esters and Carbonates

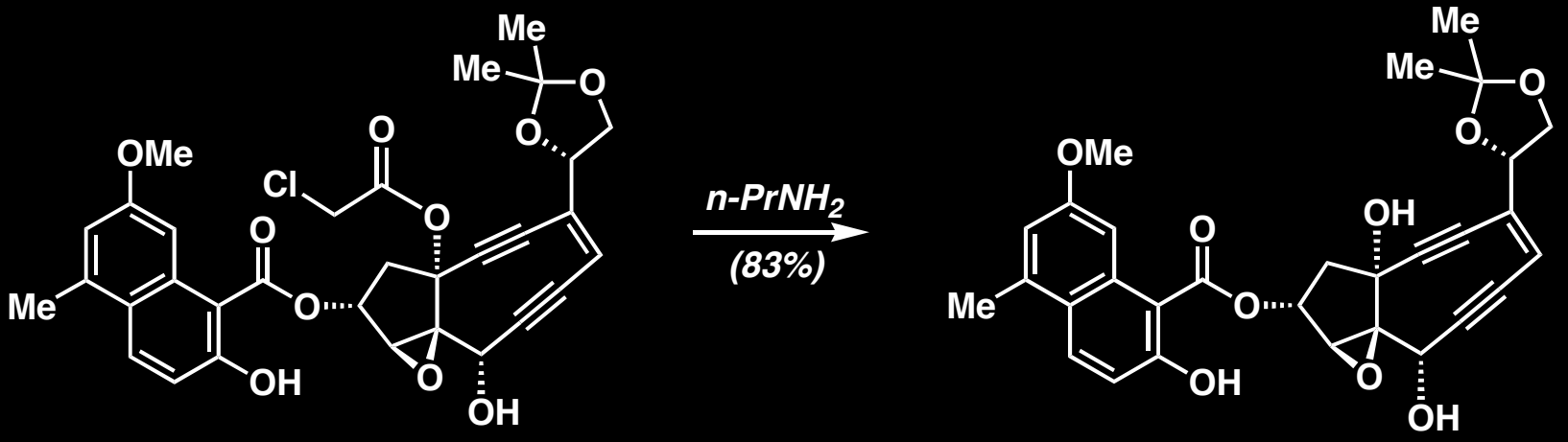
Examples of selective deprotection:

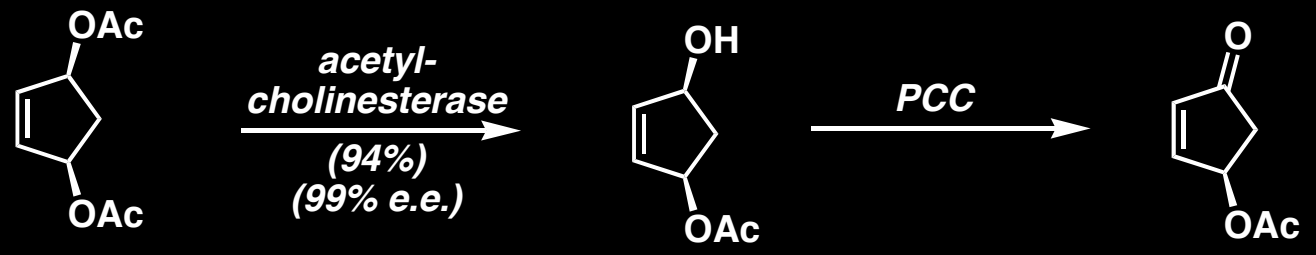


A. G. Myers and co-workers, J. Am. Chem. Soc. 1998, 120, 5319.
D. R. Deardorff and co-workers, Tetrahedron Lett. 1986, 27, 1255.

Hydroxyl Protecting Groups: Esters and Carbonates

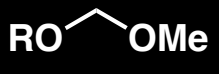
Examples of selective deprotection:



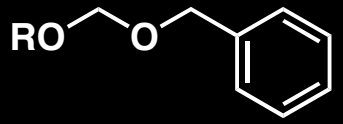


A. G. Myers and co-workers, J. Am. Chem. Soc. 1998, 120, 5319.
D. R. Deardorff and co-workers, Tetrahedron Lett. 1986, 27, 1255.

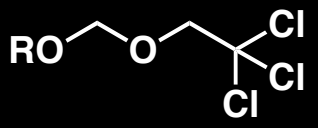
Hydroxyl Protecting Groups: Acetals



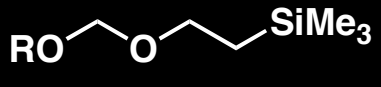
methoxymethyl ether (MOM) [cleaved with strong acid]



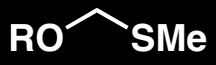
benzyloxymethyl ether (BOM) [cleaved by hydrogenation]



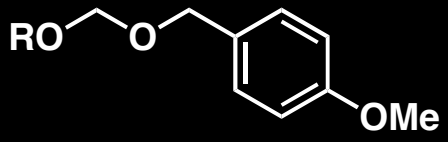
2,2,2-trichloroethoxy methyl ether [cleaved with Zn]



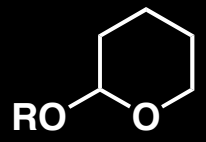
2-(trimethylsilyl) ethoxymethyl ether (SEM) [cleaved with fluoride]



methylthiomethyl ether (MTM) [cleaved with $HgCl_2$ or $AgNO_3$]



p-methoxybenzyl ether (PMBM) [cleaved with DDQ]



tetrahydropyranyl ether (THP) [cleaved with mild acid]

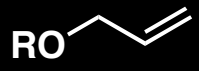
Hydroxyl Protecting Groups: Acetals

Formation of acetals:

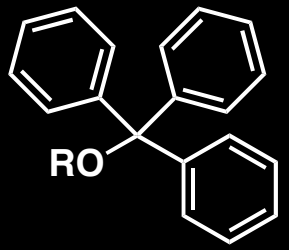
PPTS = pyridinium p-toluenesulfonate

P. A. Grieco and co-workers, J. Org. Chem. 1977, 42, 3772.

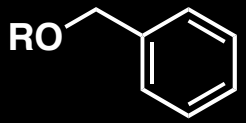
Hydroxyl Protecting Groups: Ethers



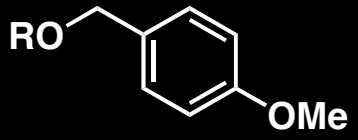
allyl ether
[cleaved with Pd/Nu]



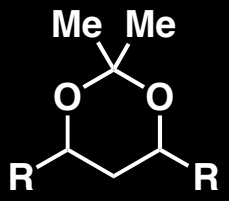
trityl ether
[cleaved by strong acid]



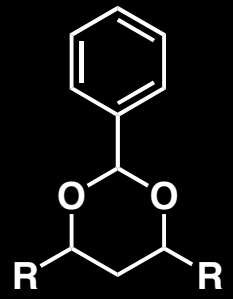
benzyl ether (Bn)
[cleaved by hydrogenation]



p-methoxybenzyl ether (PMB)
[cleaved with DDQ]



dimethyl acetonide
[cleaved with acid]

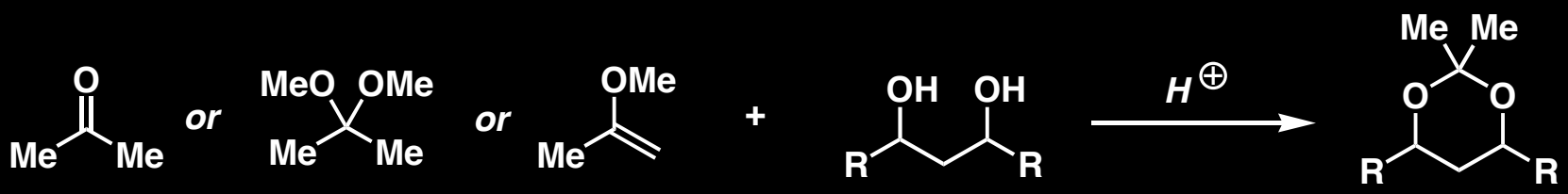


benzylidene acetal
[cleaved by hydrogenation]

Hydroxyl Protecting Groups: Ethers

Formation of ethers

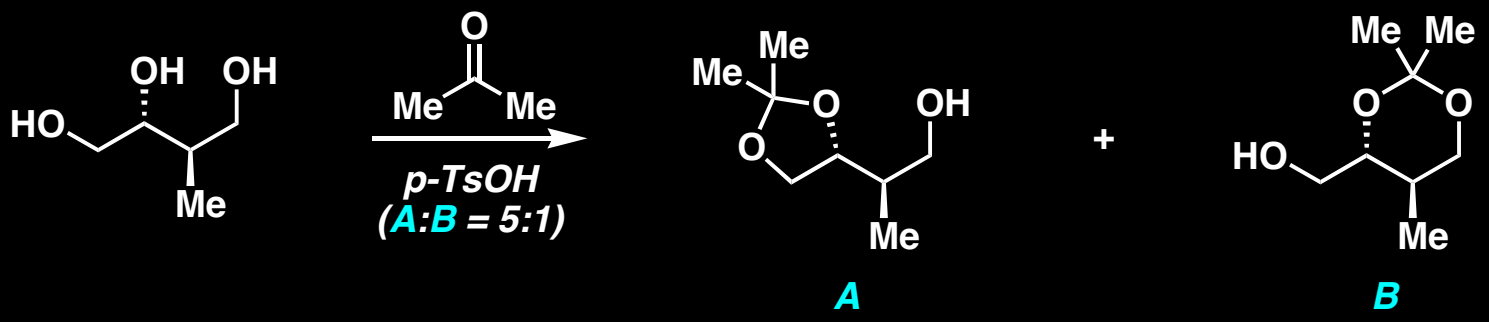
Exception is trityl groups; they require Ph_3CCl and 4-DMAP at elevated temperatures.



Concept applies to any group that can be appended to a diol.
Thus, to form a benzylidene acetal, one should use benzaldehyde.

Hydroxyl Protecting Groups: Ethers

What about polyols? Which cyclic ether will be formed selectively?



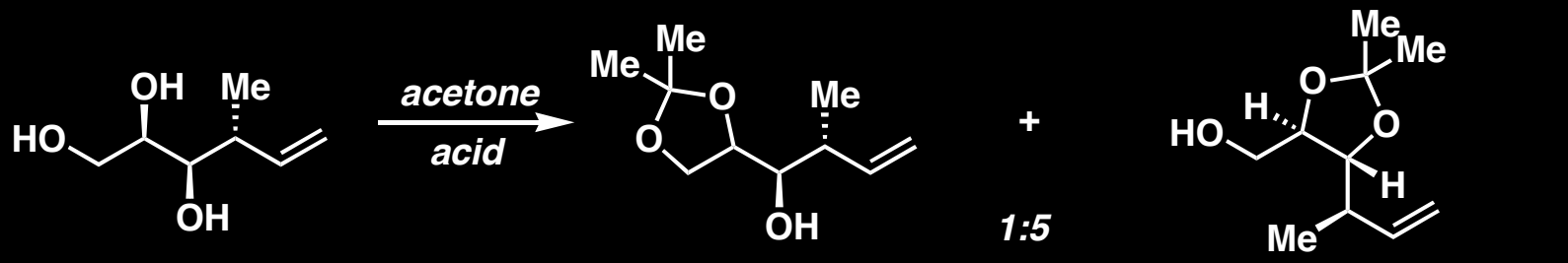
In general, simple acetonide formation with 1,2-diols occurs in preference to 1,3-diols. Note, though, that benzylidene acetals display reverse selectivity!

D. R. Williams, S.-Y. Sit, J. Am. Chem. Soc. 1984, 106, 2949.

Hydroxyl Protecting Groups: Ethers

What about polyols? Which cyclic ether will be formed selectively?

The case of a 1,2,3-polyol



Kinetic product

Thermodynamic product

In general, the more substituted acetonide is favored, especially when the substituents on the 5-membered ring are in a trans orientation; in a cis case, the less substituted acetonide might be favored.

W. R. Roush, J. W. Coe, J. Org. Chem. 1989, 54, 915.

Hydroxyl Protecting Groups: Ethers

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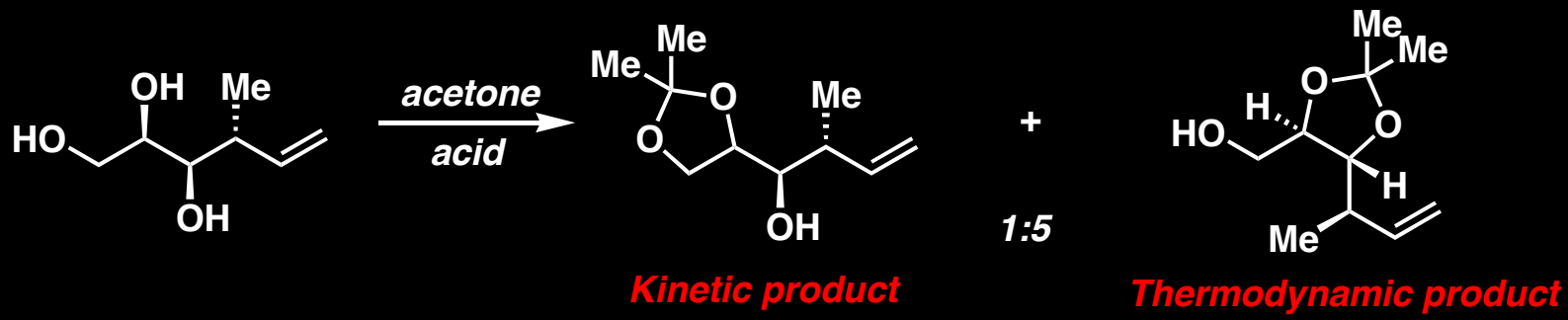

Kinetic product ***Thermodynamic product***

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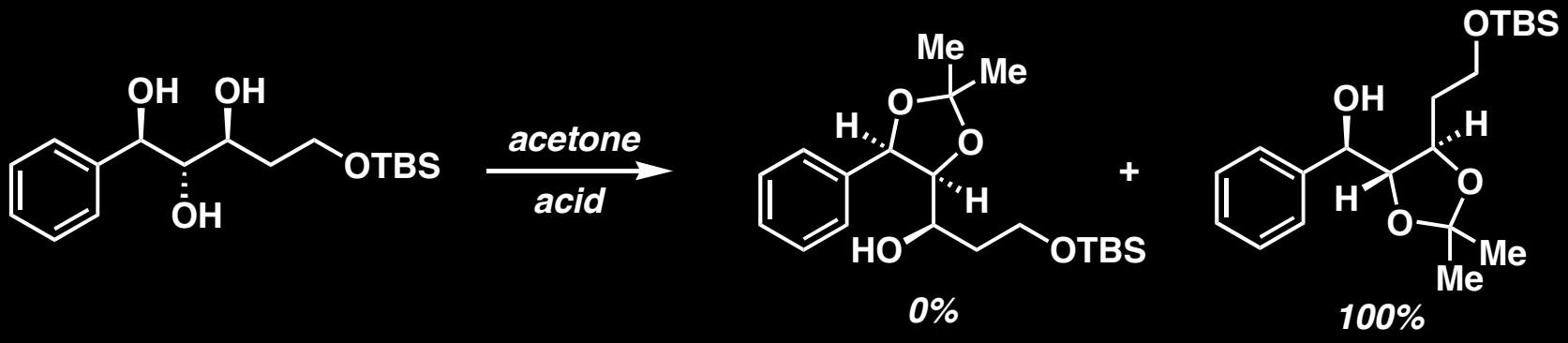
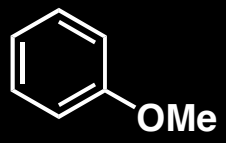


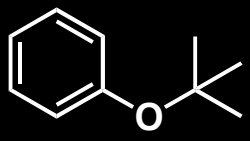
0% ***100%***

W. R. Roush, J. W. Coe, J. Org. Chem. 1989, 54, 915.

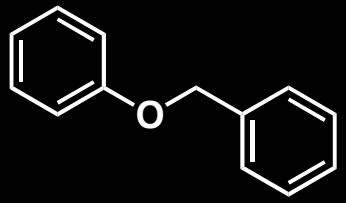
Phenol Protecting Groups



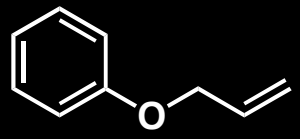
methyl ether [cleaved with TMSI, BBr_3, or 9-Br-9-BBN]



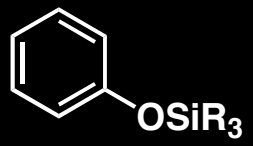
t-butyl ether [cleaved with neat TFA]



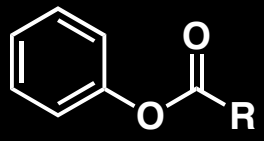
benzyl ether



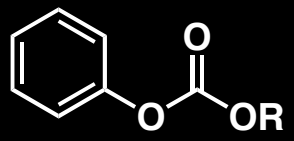
allyl ether



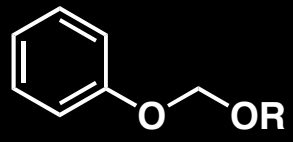
silyl ethers



phenyl esters



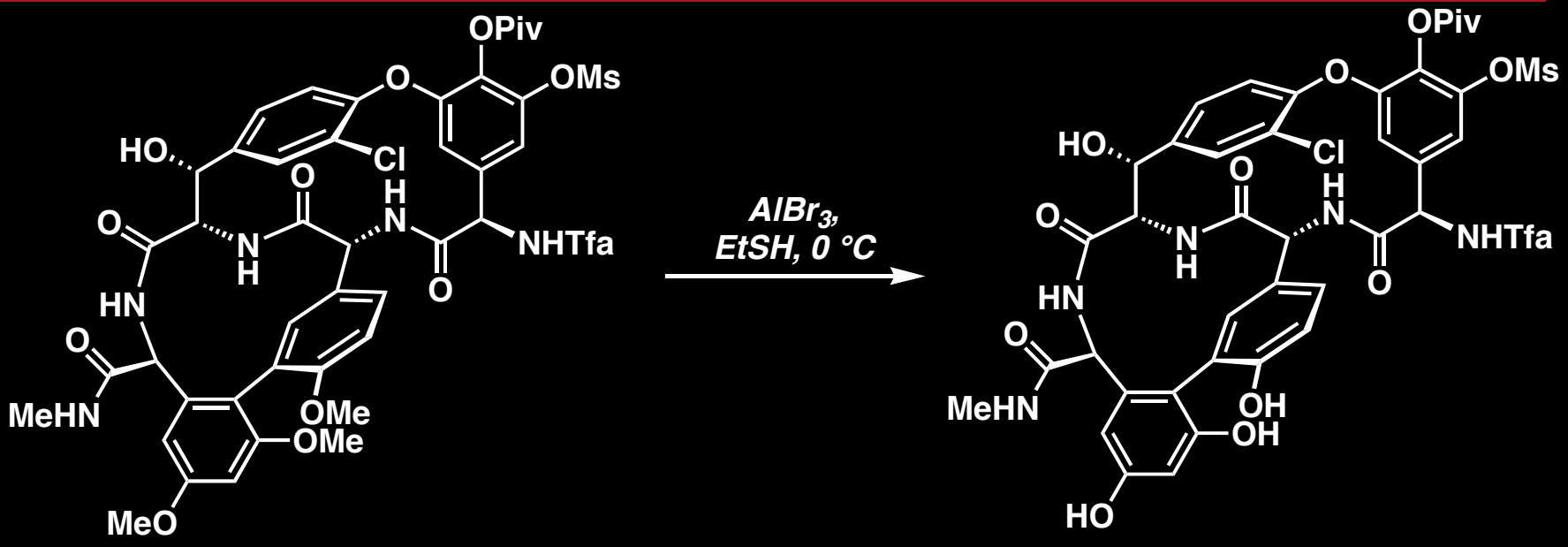
phenyl carbonates



acetals

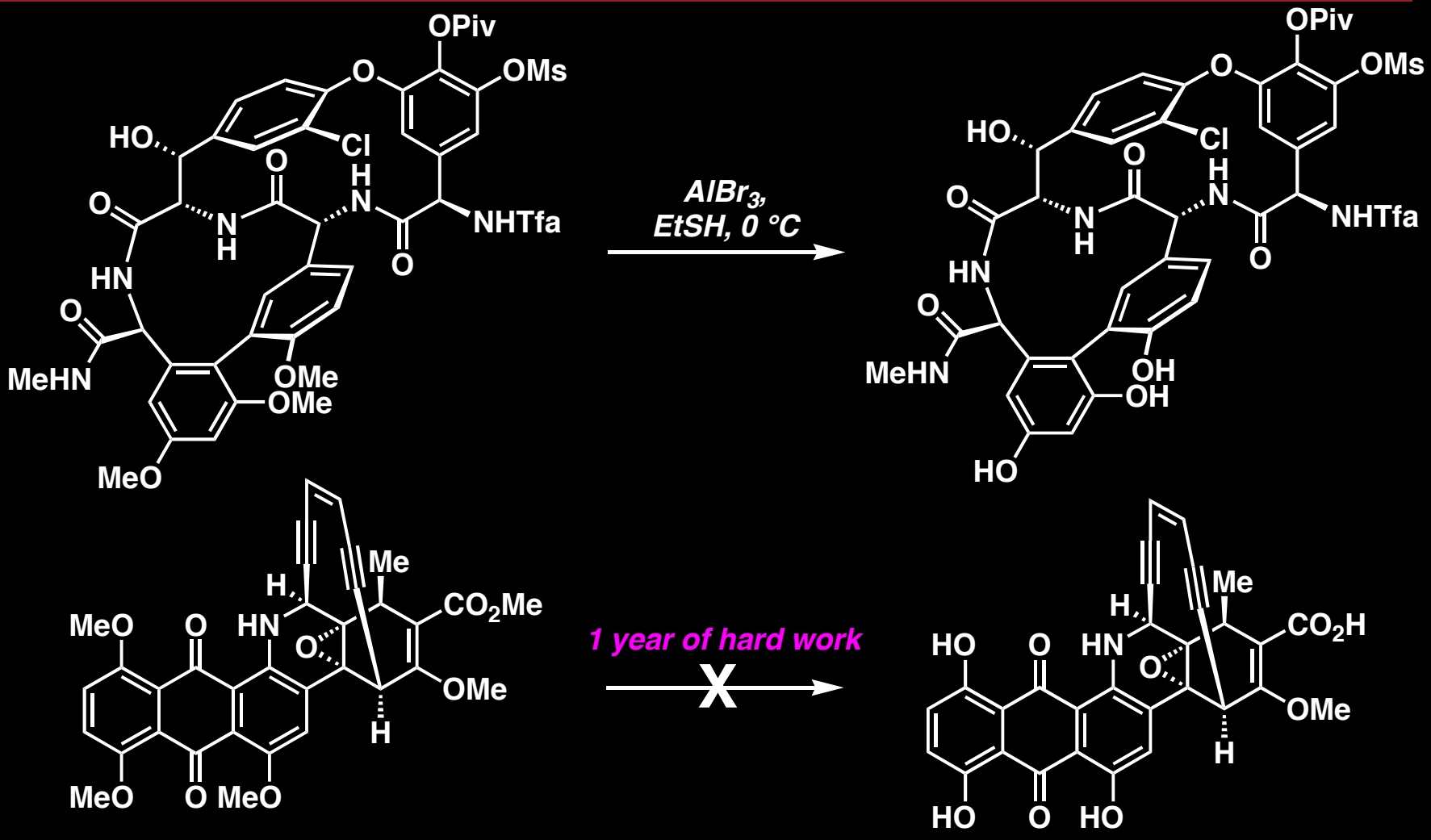
Protecting groups cleaved by base or acid are typically far more labile on phenols than a standard aliphatic alcohol. This property has important implications, as it explains why phenolic methyl ethers can be cleaved, whereas standard methyl ethers are effectively the Rock of Gibralter when it comes to deprotection (i.e., it ain't coming off)!

Phenol Protecting Groups: Methyl Ethers



D. A. Evans and co-workers, Angew. Chem. Int. Ed. 1998, 37, 2700.
S. L. Schreiber and co-workers, J. Am. Chem. Soc. 1993, 115, 10378.

Phenol Protecting Groups: Methyl Ethers



D. A. Evans and co-workers, Angew. Chem. Int. Ed. 1998, 37, 2700.
S. L. Schreiber and co-workers, J. Am. Chem. Soc. 1993, 115, 10378.

Carbonyl Protecting Groups

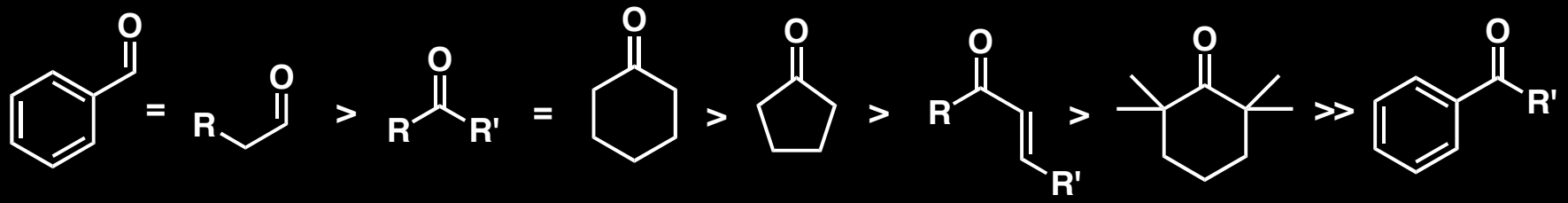
dimethyl acetal

1,3-dioxane

1,2-dioxolane

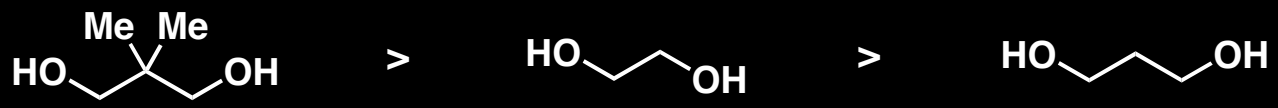
All are formed by the action of an acid with the appropriate alcohol

Reactivity order towards forming these protecting groups:

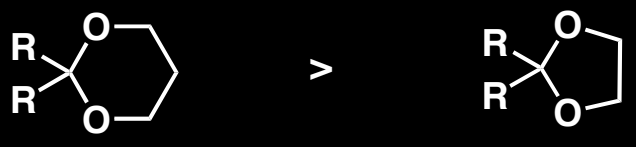


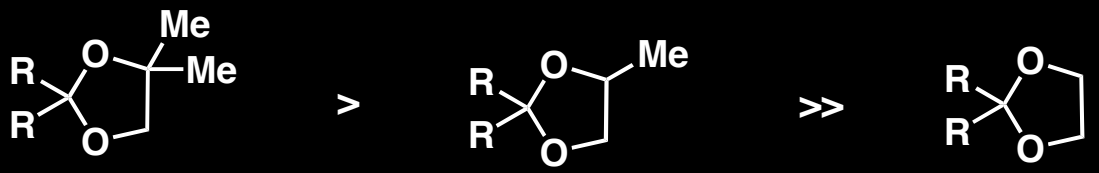
Carbonyl Protecting Groups

Rates of formation:



Rates of cleavage:

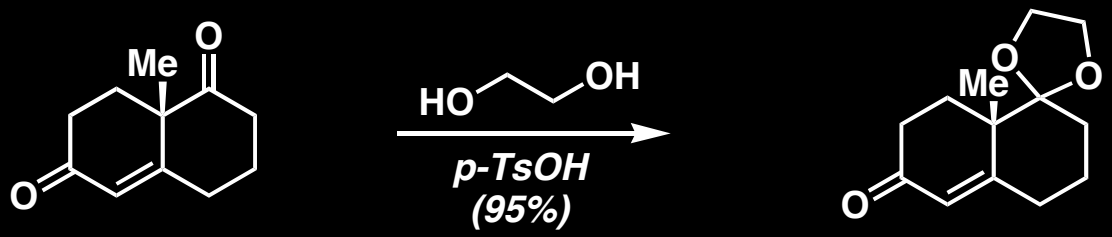




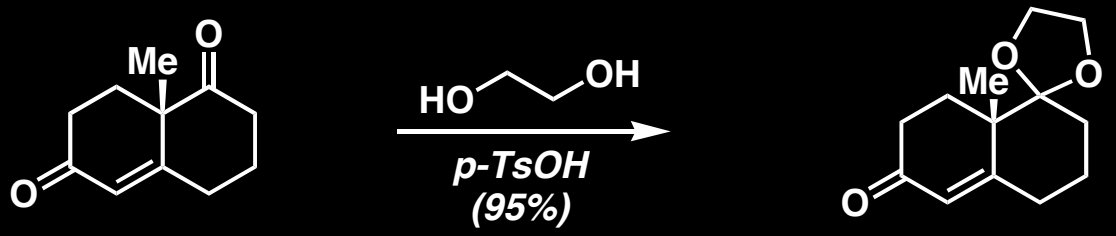
k_{rel} ***50,000*** ***5,000*** ***1***

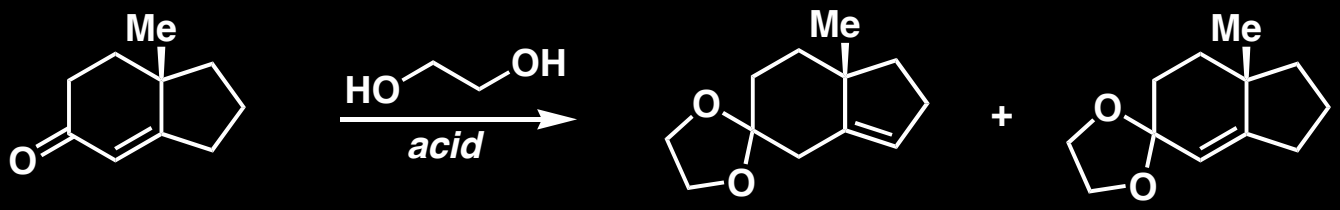
M. Ohno and co-workers, Tetrahedron Lett. 1982, 23, 1087.

Carbonyl Protecting Groups



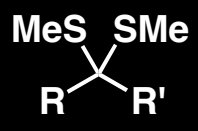
Carbonyl Protecting Groups



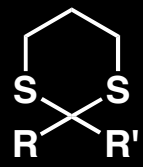


fumaric acid (pK_a = 3.03)	*100*	*0*
phthalic acid (pK_a = 2.89)	*70*	*30*
oxalic acid (pK_a = 1.23)	*80*	*20*
p-TsOH (pK_a < 1.0)	*0*	*100*

Carbonyl Protecting Groups



dimethyl thioacetal



1,3-dithiane

1,2-dithiolane

cyanohydrin

[deprotected with Hg, NBS, IBX]

Carbonyl Protecting Groups

dimethyl thioacetal

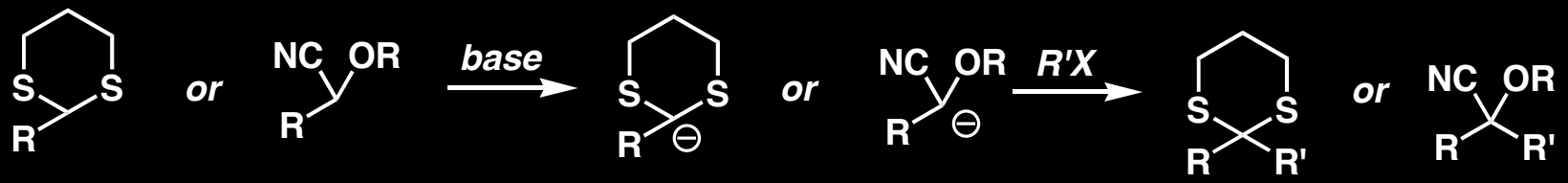
1,3-dithiane

1,2-dithiolane

cyanohydrin

[deprotected with Hg, NBS, IBX]

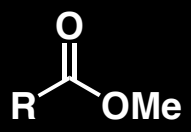
Special uses for these protecting groups:



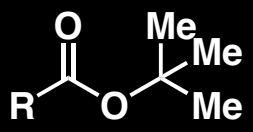
These groups turn aldehydes into nucleophiles

Umpolung = formal reversal of the polarity of a functional group

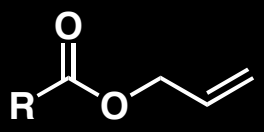
Carboxylic Acid Protecting Groups



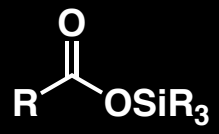
methyl ester



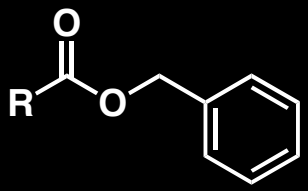
t-butyl ester



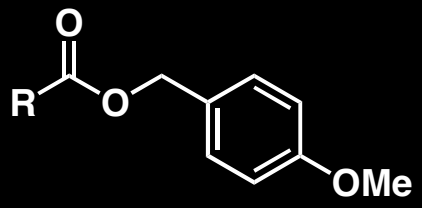
allyl ester



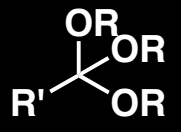
silyl ester
[must be TBS, TBDPS, or TIPS if you want to purify by chromatography]



benzyl ester

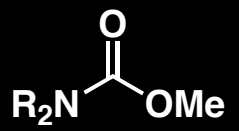


p-methoxybenzyl ester

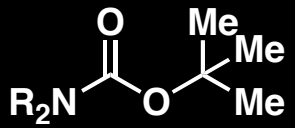


ortho ester

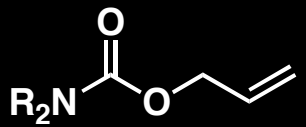
Amine Protecting Groups



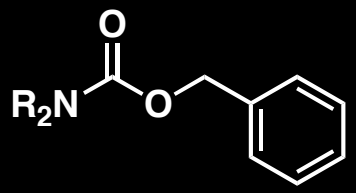
methyl carbamate



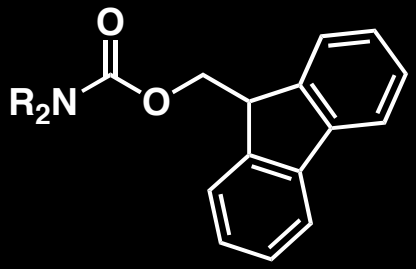
t-butylcarbamate (Boc)
[resistant to nucleophilic attack]



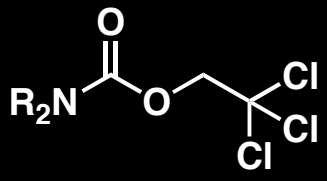
allyl carbamate (Alloc)
[cleaved with Pd]



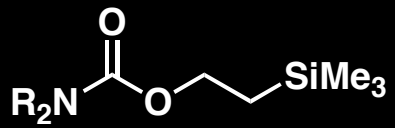
benzyl carbamate (Cbz)
[cleaved by hydrogenolysis]



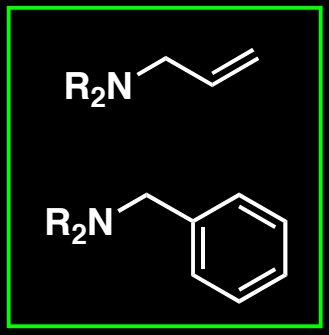
9-(fluorenylmethyl) carbamate (Fmoc)
[cleaved by mild base]



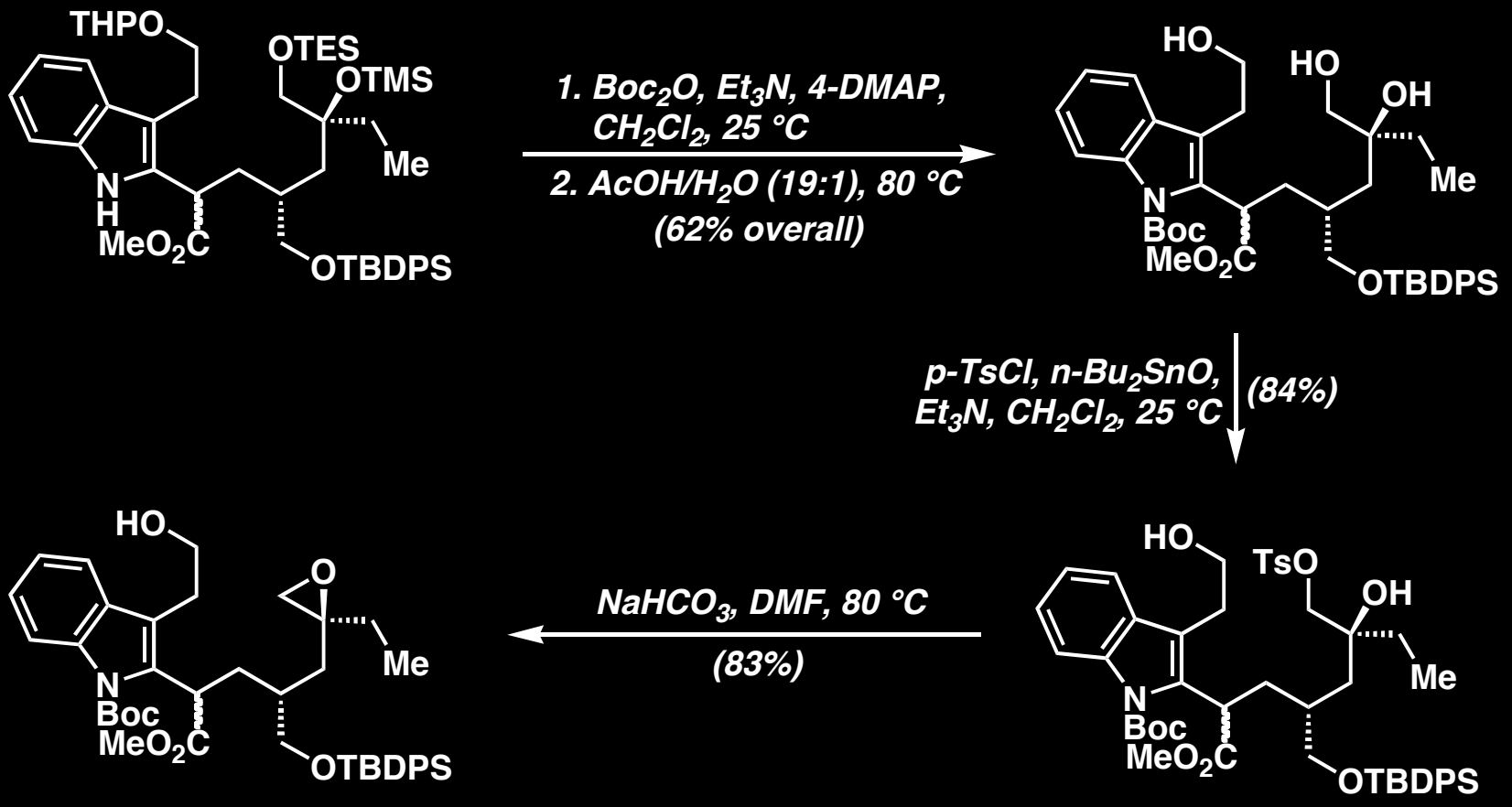
2,2,2-trichloroacetyl carbamate (Troc)
[cleaved with Zn/HOAc]



2-(trimethylsilyl) ethyl carbamate (Teoc)
[cleaved with fluoride]

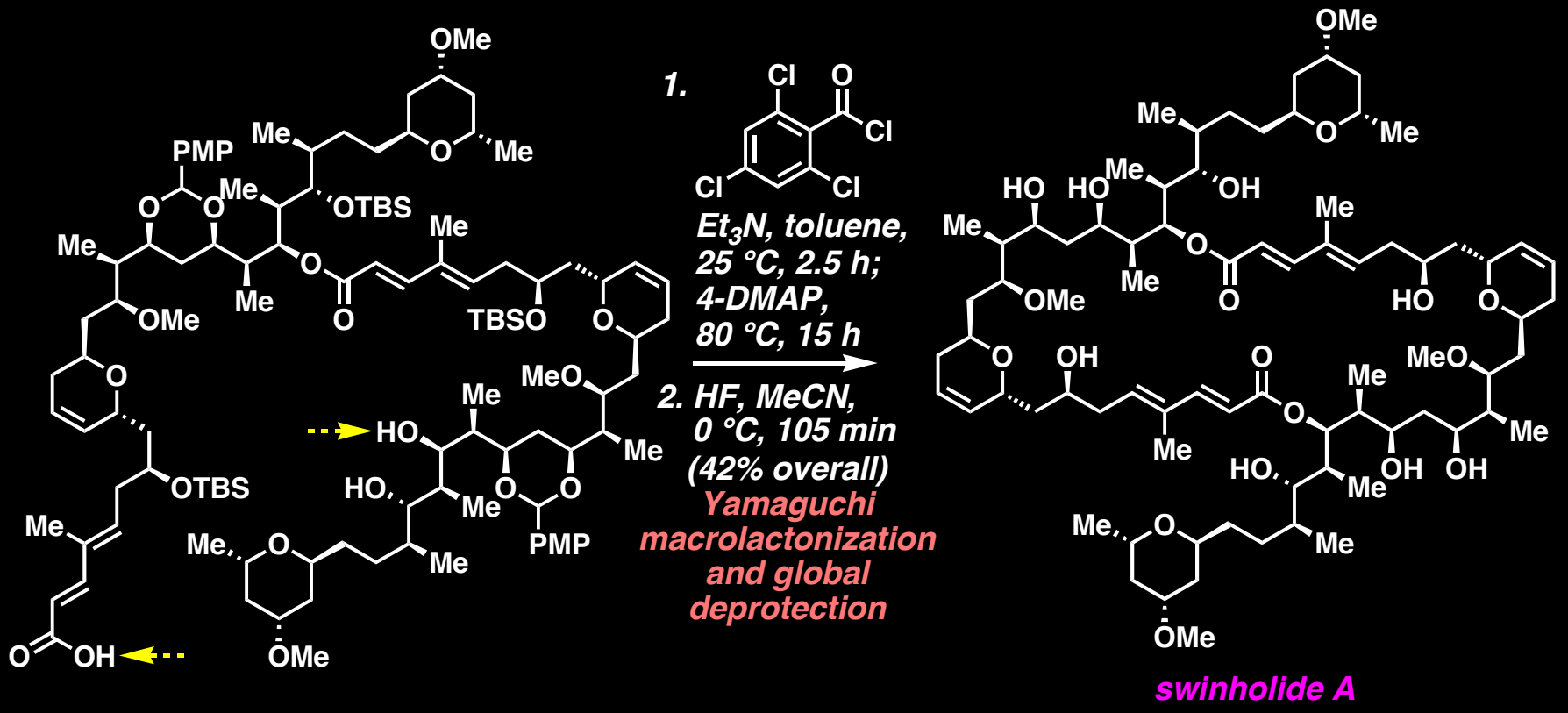


Protecting Groups: Putting it all Together



T. Fukuyama and co-workers, J. Am. Chem. Soc. 2002, 124, 2137.

Protective Groups: Sometimes They Really Are Not Needed . . .



With protecting group present on the other alcohol, dramatically lower yields observed

I. Paterson and co-workers, J. Am. Chem. Soc. 1994, 116, 9391.